Risk Management Plan
Suboxone - Subutex

Ref: NDAs 20-732 and 20-733

This risk management plan is intended to ensure safe and effective use of Subutex and Suboxone and to establish a monitoring system that will both deter and detect diversion and abuse of Subutex and Suboxone. The features of the program include:

1. Targeted product distribution and sales monitoring
2. Active surveillance for diversion and abuse, using multiple modes of information capture
3. Educational programs for patients, physicians, and pharmacists

PRODUCT DISTRIBUTION

We intend to maintain a narrow initial distribution channel, i.e. neither Subutex nor Suboxone will be placed into an automatic initial wholesaler distribution system. Initially, products will be placed into the wholesaler network based on patient demand and relative to the geographic distribution of physicians who are qualified to prescribe them under the Drug Addiction Treatment Act of 2000 (DATA).This will deter wide distribution of both products through the wholesaler channel and will allow monitoring of suspicious orders. Both products will only be made available through the wholesale system. All shipments will be monitored through the ARCOS program.

The distribution chain is designed to best serve the patients' needs while maintaining the integrity of a demand based distribution system. In summary, we are committing to a demand based system, which incorporates all federal and state regulations and laws for all levels of the distribution chain (ex. Manufacturer, Distributor, Wholesaler, Pharmacy, and Physician) as established by DEA, state regulatory authorities and federal/state law. In addition, we have put in place procedures to monitor unusual ordering patterns. We will report suspicious orders to DEA, with copies to FDA on a periodic basis as described below. We have established procedures to monitor unusual ordering patterns. All orders received will be reviewed. Reporting determination of unusual orders will be made by supervisory personnel. Any orders determined to require immediate attention by the supervisor, will be handled as such. We will report documented suspicious orders to DEA as they occur.

Only qualified physicians, as defined in the Drug Addiction Treatment Act of 2000, may prescribe Suboxone or Subutex, and only after they have notified the Secretary as required by the

Act. DEA has the authority to audit these physicians at any time to ensure that proper credentials have been attained prior to prescribing. DEA has determined as a matter of policy and announced that each District Office will audit at least two of these practitioners in their regulatory cyclic work plan.

We will provide Pharmacist educational materials through American Pharmaceutical Association publications as well as through direct mailings to pharmacies and the specially trained sales force that will be providing physician and pharmacy education. DEA has the authority to audit pharmacies at any time to ensure that proper documentation is on hand at the pharmacy to support filled prescriptions.

Wholesalers are required by federal law to implement a suspicious order monitoring system (SOMS) and to adhere to the requirements of the ARCOS system. In conjunction these two systems allow for tracking and monitoring of controlled substances both pre- and post- order. We will communicate to wholesalers that ordering of product should be based on pharmacy demand and that we will not be autoshipping the products.

Steps of Distribution System

The objective of the Ordering Process procedures is to provide a positive control that will prevent abusive ordering of Suboxone and Subutex.

1. All orders for Suboxone/Subutex will be received in our centralized Customer Service Department
2. Until such time as the product volume may demand, all Suboxone/Subutex will be distributed from a single distribution center.
3. Orders for Suboxone/Subutex will be processed separately from all other products.
4. All orders for Suboxone/Subutex will be billed separately.
5. Only orders from direct accounts may be processed and fulfilled. Drop shipments will not be allowed except under emergency situations, and then only after supervisory approval. Daily override reports are generated and require management review and signature to ensure full compliance.
6. Each order quantity of Suboxone/Subutex will be reviewed prior to processing. Until ordering history can be established by individual account, initial monitoring levels will be established. These criteria may increase or decrease once normal ordering patterns can be established and documented.

Suspicious Order quantity levels have been established initially based on the following information and/or hypotheses:

- DATA allows for no more than 30 patients being treated per physician or group practice at any point in time.

- Based on information received from CSAT, AAAP, APA and ASAM it is assumed that initially no more than 2,000 physicians will qualify for prescribing Suboxone/Subutex for a Q4 launch.
- Induction Dosing – it is assumed that physicians will prescribe an average 8mg dose on day 1 and 16mg on day 2. Depending on the physicians' assessment, this dosage may vary.
- Maintenance Dosing – it is assumed that 16mg Suboxone may be an average dose, with a range of 4mg to 24mg per day.

Wholesaler Monitoring Recommendations

Physician Ordering:
We will provide recommendations to individual wholesalers concerning Suspicious Physician ordering levels to be used in conjunction with current suspicious order monitoring currently in place at the wholesaler as required by DEA regulation. Our recommendations to wholesalers for suspicious order monitoring quantity limits are based on the factors noted above and are presented on a per- month, per-physician basis, as follows:

Subutex
two bottles (30 tablets per bottle) of 2mg Subutex
or
two bottles (30 tablets per bottle) of 8mg Subutex
or
three bottles in total with neither 2mg nor 8mg orders greater than two bottles.
The three-bottle total is in specific response to the flexibility required using 2mg and 8mg tablets during induction dosing.

Suboxone
fifteen bottles (30 tablets per bottle) of 2mg Suboxone
fifteen bottles (30 tablets per bottle) of 8mg Suboxone

Pharmacy Ordering

We will provide recommendations to individual wholesalers concerning suspicious pharmacy ordering levels to be used in conjunction with Suspicious Order Monitoring systems currently in place at the wholesaler as required by DEA regulation. Wholesalers will be provided with geographic prevalence rate (by state) of physicians qualified to prescribe Suboxone/Subutex, and of narcotic treatment programs from SAMHSA's Substance Abuse Treatment Facility Locator.

Wholesaler Ordering

Subutex

Our initial implementation of suspicious order monitoring of wholesalers for Subutex orders will be established nationally based on 2,000 physicians, 15 patients per physician, two tablets of either 2mg or 8mg or a total of three tablets (assuming no more than two tablets of either strength). Given these assumptions, suspicious ordering limits of Subutex would be placed at 1,000 bottles of Subutex per week of either 2mg or 8mg strengths, or 1,500 bottles of 2mg or 8mg tablets in total, without exceeding the limit of either strength. If these limits are exceeded and the number of qualified physicians remains below 2,000 we will undertake a review of all shipments with the director of the Active Surveillance program who will suggest appropriate actions for more detailed monitoring.

Suboxone

Based on our initial assumptions of 2,000 physicians, 15 patients per physician, 2-tablets/day/patient maximum, total demand would be 420,000 tablets per week or 14,000 bottles per week demand for Suboxone. Initially, we would set wholesaler limits at 2,000 bottles/week of Suboxone per wholesaler distribution center. These limits will be adjusted based on historical ordering levels over time.

Note that ordering levels established in this document are based on our initial assumptions. We anticipate that over time the number of qualified physicians will increase from 2,000 to over 5,000 as will the number of filled treatment slots (from 15 to a maximum of 30). In addition, dosing regimen will be highly variable by patient based on a number of factors and will ultimately be determined by the physician in managing each patient's individual progress.

All orders received will be reviewed. Quantities will be checked against the quantities processed week-to-date. If the order is unusual at this point, it will be referred to the Supervisor/Manager. If there is a reasonable explanation for the order (i.e. customer hadn't ordered in several weeks, backorder release etc.) it will be processed. If necessary, the Supervisor or Manager will contact the customer to investigate further. If the investigation is not satisfactory, the matter will be referred to a designated management person who will determine if reporting to DEA is warranted. The original order will be held pending and remain unprocessed awaiting final disposition from management. If the order is not approved, the original order will be filed in the Suspicious Order file. If the order is approved, the written approval is attached to the order with Customer Service management's signature.

We will send the DEA a report of suspicious orders and the disposition of such on a quarterly basis. Copies of these reports will be included in periodic reports to the FDA.

Both Suboxone and Subutex will be distributed by wholesalers.

As noted previously wholesalers will be provided with geographic prevalence rates of qualified physicians and location of qualified treatment facilities through the CSAT Database. Wholesalers will be responsible to set ordering limits based on market demand, historical ordering, and their own Suspicious Orders monitoring procedures. Given the wide span of geographic control for wholesalers, monitoring wholesalers on a geographic basis will not be possible. Instead, we will defer to the procedures and guidelines documented previously in this paper.

We have consulted with experts in the field and with the Center for Substance Abuse Treatment, and have carefully considered methods of ensuring that induction doses are readily available to physicians in their offices. As a result of those discussions we have determined that physicians should be provided with two options for such doses. Many physicians are reluctant, or simply refuse, to maintain a stock of controlled substances in their offices for a variety of valid reasons, and it would be inappropriate to insist that they do so. Similarly, many physicians will wish to dispense most induction doses from their offices. Consequently we intend to include in an educational package, which will be provided to all qualified physicians, instructions for both scenarios, both of which will provide for supervised induction. The physician educational material is included as attachment 5. Additional educational material will be implemented following approval of the NDAs and submitted for review.

1. For those physicians who wish to maintain a stock of tablets in their offices for induction we will provide information in the initial education package to enable the physician to request that supply. After verifying that the physician is qualified and practices in a state where this is applicable, we will provide them initial stock and information on how to obtain replacement stock. Physician qualification will be verified via continuous communication with CSAT and DEA who are responsible for determining Physician qualification. DEA has established a method of verification via their existing database and CSAT will maintain a database of qualified physicians. Additionally, we will provide these physicians with an educational package centered on the Federal and local compliance issues of dispensing, storing, record keeping and maintaining inventories of controlled substances. A web address (www.suboxone.com) and a toll-free (1-877 SUBOXONE) (1-877-782-6966) number will be included in this packet to address any of their follow-up questions, including information on state-by-state regulations for physician office-based dispensing.

2. For those qualified physicians who do not wish to maintain a stock of tablets in their offices for induction or who practice in a state where this is not allowed, we will

provide them a request form for initial dose rebates or coupons (limit 30), in the initial education package. Under this plan physicians will provide each new patient with a prescription accompanied by the pharmacy coupon, with instructions to return to the physician's office for dosing and monitoring before the follow-up maintenance prescription is written, as permitted by the applicable state laws. Through all promotional and educational material, we will stress the importance of supervised induction, and recommend that physicians coordinate with a local pharmacy prior to initiating treatment to ensure product will be available. For those physicians who do not currently have a relationship with a local pharmacy, we will offer assistance in establishing such a relationship through a web site (www.suboxone.com) and a toll-free (1-877 SUBOXONE) (1-877-782-6966) number.

The staffing for the call center will be Customer Service professionals who are already taking calls for various programs. They already have customer service knowledge, systems training and professionalism. We are in the process of building an education module to train these individuals on the specific product knowledge they will require for this program. The time of operation is as follows: Peak Hours (manned by live agents) 9:00am – 9:00pm EST, Monday through Friday, Off-Peak Hours (not manned by live agents, IVR only) 9:00pm – 9:00am Monday through Thursday and 9:00pm Friday – 9:00am Monday EST. This staff will be trained to answer general product questions. For more technical/scientific questions or to report adverse events; calls will be transferred to our in – house Drug Information and Drug Safety Departments. Additionally, this Call Center will be supported by a Fulfillment Center to meet requests for printed Educational and or Promotional materials pertaining to the products. The pre-approval script that the Call Center Staff will utilize is included at Attachment 1. The post-approval script will be submitted upon drug approval/approval of final label.

The size of shipments of Subutex and Suboxone to wholesalers will be limited based upon the demand level observed in the service area. Once normal demand levels have been established, wholesaler orders that exceed historical trends will prompt a more detailed company review of respective wholesalers' ordering patterns taking into account corresponding changes in geographic dispersion or number of their pharmacy or clinic accounts, before these orders will be filled. All participating wholesalers are required to maintain, on an ongoing basis, copies of pharmacy shipment reports detailing product movement by pharmacy and quantity. Prior to shipment of any product to a physician, we will consult the DEA Database to assure the physician's name, address, and registration is current, that the physician is qualified to prescribe the products, and to determine that the requested ship-to address is the registered address. One criterion to determine suspicious orders at the wholesale level is a review of the relationship of Subutex to Suboxone order quantities.

Subutex and Suboxone are listed in Schedule III of the Controlled Substances Act. Schedule III substances are subject to DEA's Automation of Reports and Consolidated Orders System

(ARCOS). ARCOS is an automated, comprehensive drug reporting system that monitors the flow of DEA-controlled substances from their point of manufacture through commercial distribution channels to point of sale or distribution at the dispensing/retail level – hospitals, retail pharmacies, practitioners, mid-level practitioners, and teaching institutions. ARCOS accumulates these transactions, which are then summarized into reports, which give investigators in Federal and state government agencies information that can then be used to identify the diversion of controlled substances into illicit channels of distribution. Under ARCOS:

a. We will report all synthesizing activities, inventories, acquisitions, and dispositions of Subutex and Suboxone to ARCOS.
b. All distributors/wholesalers will report inventories, acquisitions, and disposition of Subutex and Suboxone to ARCOS
c. All distribution of Subutex and Suboxone at the pharmacy and practitioner level is controlled by existing DEA regulation designed to limit diversion. DEA publishes practitioner and pharmacy manuals as it implements regulations pertaining to the handling of these products.

Managed care and mail order pharmacies will be given educational materials related to the Drug Addiction Treatment Act as well as Pharmacy and Physician educational materials. Mail order pharmacies will be requested to verify delivery of all prescriptions.

Individual wholesalers, pharmacists, etc, will report suspicious orders directly to DEA as required by State and Federal regulations.

ACTIVE SURVEILLANCE

The program of active surveillance will be administered by the Substance Abuse Research Division at Wayne State University (SARD). It will focus on active collection of information from individuals at risk for abusing buprenorphine collected via treatment programs, private practitioners, and ethnographers, media, and internet; as well as monitoring of passively collected data from sources such as DAWN, CEWG, and other sources

Individuals at risk for abusing buprenorphine

Naloxone has been added to buprenorphine in the formulation Suboxone to guard against its parenteral use by individuals physically dependent on opiates. It should be noted that Suboxone is the formulation to be used in the vast majority of patients. Additionally, Subutex is likely to precipitate withdrawal if parenterally administered by individuals who are physically dependent upon opiates and have recently taken a dose of an opiate. This is because buprenorphine is a partial agonist with greater affinity for and slower dissociation from the opiate mu receptor. Its limited agonist effects may be sufficient to produce some relief for individuals undergoing opiate withdrawal but not like that produced by full agonists such as heroin or methadone. For these reasons the diversion of both preparations of buprenorphine is unlikely to find a significant market in individuals physically dependent upon opiates.

There are, however, individuals who are opiate "chippers" who find the psychoactive effects of opiates reinforcing but who are neither tolerant nor physically dependent. In these individuals both Suboxone and Subutex may have some appeal. A recent study (Comer, et al 2002, Drug and Alcohol Dependence 66 (Supplement 1), S35) has shown that in such individuals the reinforcing effects of parenterally administered buprenorphine alone or in combination with naloxone in the ratios to be used in Suboxone were indistinguishable. Thus, although the dosage of naloxone has the ability to precipitate withdrawal in individuals physically dependent upon full agonists, it is not at a high enough dosage to block the reinforcing effects of buprenorphine even when administered intravenously. Thus, the diversion of both preparations of buprenorphine could find a small market among those who are opiate "chippers". It is impossible to accurately estimate the size of this population but most experts feel that it is a small unstable group.

The relative safety of buprenorphine, in comparison to full mu opiate agonists, could encourage some youthful poly-drug abusers to experiment with the drug. In this population it might be administered sublingually and because of the absence of tolerance produce an opiate effect. Taken parenterally it would produce an even greater effect. It is, however, unlikely to appeal to the "Club-Drug Set" who are looking for stimulation rather than sedation. Our Club-Drug expert co-investigator (Dr. Boyd) as well as representatives of the Dance Safe organization have stated that opiate drugs are rarely if ever found at Club Drug parties or Raves. A final factor limiting

the use of Suboxone particularly among young drug abusers will be its price. Individuals, who are being prescribed Suboxone, unlike methadone, will most likely be paying for this medication out-of-pocket. Diverted Suboxone would sell at a much greater price than many of the currently abused opiate prescription drugs. Thus, its relative cost may serve as a barrier to its diversion to young poly-drug abusers.

In summary the most likely groups of people to abuse buprenorphine are those who are currently opiate chippers and a small proportion of the poly-drug abusing youth sub-culture. SARD's prediction is that because of the widespread publicity concerning the introduction of buprenorphine products onto the market there will be an initial phase of experimentation. If people who are physically dependent upon heroin or methadone mistakenly take it, naloxone-precipitated withdrawal will likely very quickly give Suboxone a "bad" reputation on the street. Hopefully this will discourage people who are only chipping heroin from experimenting with Suboxone since they may be unsure of their physical dependence status.

Information Sources

Post-Marketing Surveillance Areas

SARD will divide the country into "Surveillance Areas." SARD assumes that illegally marketed Subutex and Suboxone will make their entrée in areas that have a regular supply of buprenorphine products, i.e., areas that have physicians who prescribe them for patients with opiate addiction. Therefore, the distribution of addiction medicine physicians will be the basis for setting up surveillance areas.

As of July 11, 2002, we have identified 3,337 private physicians who may qualify to prescribe Suboxone/Subutex when approved for the treatment of opiate dependence. Mapping software has divided these physicians into 24 distinct tentative territories, each with approximately 139 physicians (Table 1). Territories, however, vary substantially in size. They range from just 2 miles in radius (Jersey City) to 125 miles (Nashville/Memphis/St. Louis). The average is 66.2 miles. Many of the smaller territories encompass communities that contain the highest proportion of opiate treatment admissions per 100,000 population. Using these territories has the advantage of permitting SARD to compare surveillance findings in each area with the actual Subutex/Suboxone sales volume for the area.

Table 1
Geographic Territories

Territory	Qualified Physicians per Territory	Radius
Boston	169	40
Bridgeport	132	35
New York	148	21
Jersey City	148	2
Newark	130	29
Philadelphia	156	37
Washington, DC/Baltimore	175	38
Chattanooga/Atlanta/Columbus	140	70
Orlando/Tampa/Miami	141	78
Detroit	158	63
Chicago	148	33
Milwaukee	132	59
San Antonio/Austin/Houston	125	122
Dallas/Oklahoma City	130	123
Los Angeles	133	67
San Jose	127	82
Anaheim	131	23
San Diego	130	71
Sacramento	128	103
Seattle/Portland	134	80
Nashville/Memphis/St. Louis	128	125
Cleveland/Pittsburgh	135	92
Indianapolis/Dayton/Louisville	132	83
Augusta/Charlotte/Knoxville	127	112

Substance Abuse Treatment Programs

Among the best sources of information regarding current drug abuse practices on the street are drug users themselves. A convenient place to interview drug abusers is during the intake process in treatment clinics. SARD will ask a sample of substance abuse programs to add two instruments specifically designed for this project (*Product-Familiarity Interview* and *Adverse Event Information*) to their intake process (see, Data Collection Instruments and Report Formats). These instruments, which are described in the Instruments section of this document, are designed to determine whether treatment applicants have heard of Subutex or Suboxone and know of any abuse of the products.

Year One Sample

Throughout the project, SARD expects to maintain a total sample of 60 treatment programs. In the first year of the project, programs will be selected to provide a specifically determined geographic distribution based on the previously described surveillance areas. A minimum of one treatment program will be selected to participate in the project from each of the cities in the surveillance areas. In addition to programs in cities, SARD will recruit programs from suburbs located within these same areas. Although rural communities tend to be underserved when it comes to substance abuse treatment, SARD will attempt to recruit programs that draw clients

from rural areas. Because Subutex and Suboxone are likely to be used in the treatment of opiate dependent adolescents and may have potential for abuse by this population, SARD will emphasize adolescent treatment programs.

Every attempt will be made to recruit from the National Institute on Drug Abuse's (NIDA) Clinical Trials Network (CTN), which currently has a network of 38 treatment programs in 11 of the surveillance areas. More programs in 3 different regions of the country are to be added in the next few months. Because of its stake in having buprenorphine adopted by the treatment field, NIDA has agreed to assist SARD in recruiting treatment programs by making it a recognized activity of the CTN. SARD will invite these programs to participate first because SARD has an established relationship with them and second because they are experienced in collecting data. The remaining programs will be selected with the aid of the Substance Abuse Treatment Facility Locator Web page maintained by the federal Substance Abuse and Mental Health Services Administration.

Years Two through Five

In the remaining 4 years, SARD staff will recommend that treatment programs be added or deleted depending on buprenorphine use patterns uncovered during the earlier periods. The Advisory Group organized for the Subutex/Suboxone project will review and approve any changes in sampling.

Product-Familiarity Interview

The interview questionnaire concerning Subutex/Suboxone abuse will be incorporated within the regular information-gathering process that treatment programs use during intake of new clients. This strategy is designed to avoid having the client discover the focus of the study and to avoid stimulating interest in the drug. This strategy has been used by SARD in previous studies.

The interviews will be conducted with all persons being considered for admission to participating treatment programs over a 3-year period. In addition to gathering basic demographic information (age, sex, race ethnicity, years of drug use, drug for which treatment is being requested), the interview will consist of questions dealing with the treatment applicants' familiarity with a list of drugs, knowledge of their street availability, and their personal knowledge of the abuse of the drugs. The list will contain, in addition to Subutex® and Suboxone®, the analgesic Buprenex®, and generic buprenorphine.

Product Familiarity List

OxyContin
Tofranil
Methadose
Oxycodone
Vicodin
Buprenex

Subutex
Nardil
Methadone
Buprenorphine
Imipramine
Dolophine
Suboxone
Phenelzine

We expect that the average program will conduct eight interviews per month, which will yield approximately 29,000 over the 54 months that these interviews will take place. All questionnaires will be sent to SARD monthly and entered along with a 20% re-entered for quality control. A copy of the Product Familiarity instrument is included at Attachment 6.

Private Practitioners

Physicians who have notified CSAT of their intention to prescribe opioid drugs for the treatment of opiate dependence will be invited to participate in the project. With the list current at the time the project begins, SARD will send out letters to each of these physicians asking them to participate. Each month, SARD will send letters of invitation to those physicians who are newly added to the list. Those who are interested will be asked to return an acceptance form. Each quarter, a sample of 10% of those physicians who chose to participate, with oversampling of those in rural areas or small towns, will be sent a brief questionnaire that requests any instances of abuse or inappropriate use of buprenorphine-related products they have observed with their patients. Participating physicians will be reimbursed for the time they spend filling out the questionnaire. The methodology will involve sampling-with-replacement, so it is possible that a physician will be polled more than once. In addition, every physician who receives a letter of invitation will be provided a toll-free number to call to report any suspicion of abuse or inappropriate use.

Ethnographers

Trained substance abuse ethnographers will be used to monitor local drug markets and drug-using networks in areas where Subutex/Suboxone is likely to be used. There is a network of trained ethnographers in many US cities who are part of a NIDA sponsored group (see, Community Epidemiology Work Group below). Ethnographers are skilled at getting information about recent changes in drug use patterns. There are also Community Health Outreach Workers (CHOWs) in many parts of the country, who conduct street HIV prevention activities with intravenous drug users.

Attachment 2 presents a list of individuals and organizations that can provide ethnographic services to the project. SARD will recruit 10 ethnographers/CHOWs from this list, who will each be asked to conduct unstructured street interviews in the course of their street surveillance activities. SARD already has gotten commitments from three of the CEWG associated ethnographers. SARD also has been provided a list of outreach programs funded by CSAT's Division of Practice and Systems Development. The Division has recommended several of their grantees for inclusion and has volunteered to answer grantee inquiries about the surveillance project.

Quarterly, ethnographers/CHOWs will provide SARD with a summary report of the drug scene in their area, with special emphasis on buprenorphine availability and abuse (see, Data Collection Instruments and Report Formats).

They will be encouraged to use the *Product-Familiarity Interview* in their fieldwork. However, some of the street workers may feel that using a structured questionnaire would disrupt their informal approach to gathering information and prefer not to use the *Interview*. Nevertheless, they will be asked to use a set of questions developed by SARD to guide their street interviews (see, Data Collection Instruments and Report Formats).

On average, street ethnographers attempt to enlist 30 to 40 key informants in their surveillance projects at any one time. SARD will ask the ethnographers to interview the entire group of key informants quarterly. One of the members of the Advisory Group for this project (Carol Boyd, RN, Ph.D.) has done extensive street ethnography in the past. She will take responsibility for identifying, recruiting, and training ethnographers.

Club Drug Parties and Raves

SARD originally proposed to employ DanceSafe to monitor buprenorphine use at club drug parties and raves. DanceSafe is a nonprofit, harm reduction organization promoting health and safety within the rave and nightclub community. They currently have local chapters in 24 cities throughout the U.S. SARD has reconsidered the value of monitoring club drug parties and raves to determine whether attendees are using buprenorphine. It is SARD's conclusion that this activity is both unnecessary and potentially dangerous. First, SARD has conferred with several national experts on the drug use patterns at club drug parties and raves. These individuals, who have been following the drug use at these affairs, have stated that it is their opinion that opiate drugs are not appealing at these events. The drugs most commonly used at raves and club drug parties are those with both stimulant and hallucinogenic activity (MDMA, MDA, etc.), stimulants (amphetamines), or classical hallucinogens (LSD, Mescaline, etc.). Sedative hypnotic drugs and opiates are not generally found at these affairs. It would thus appear that it would be more fruitful to use post-marketing resources in other surveillance activities.

The second concern that SARD has is that monitoring for buprenorphine use at raves using DanceSafe personnel has risks. Many of the people involved with the harm-reduction activities at

raves are themselves active club drug users. They simply agree that they will not use drugs on the nights when they are working at a rave. Although SARD does not believe that this population is likely to find the pharmacological effects of buprenorphine appealing, bringing this new drug to their attention might engender some interest in experimenting with it to test its effects. Obviously, there are risks associated with non-opiate tolerant individuals experimenting with buprenorphine particularly in combination with alcohol.

Finally, since adolescents entering treatment will be interviewed at 29 sites across the United States SARD believes that it will detect buprenorphine abuse among those who are likely to attend club drug parties and raves. These interviews should yield the same information regarding the use of buprenorphine in the adolescent or young adult population, but in a more cost-effective manner.

Media Surveillance

There already are a surprising number of Web sites that deal with buprenorphine in its various formulations. SARD conducted a simple Internet search to begin developing a methodology for either monitoring the web ourselves or selecting the topics and key words that it would want a commercial Web monitoring service to use, if it contracted out the searches. This simple search of the Web (using the Google™ search engine) showed that there are almost 14,000 sites where buprenorphine or related products are mentioned. However, the vast majority of them are straightforward discussions of the clinical uses of the drugs. Our survey of the Web shows that those sites that normally provide information geared to "recreational" users, such as erowid.org, and hightimes.com do not yet mention buprenorphine. During the first month of the project, SARD anticipates spending about 20% of staff time familiarizing itself with relevant Web sites, chat rooms, bulletin boards, forums, and Web-based news sources. Simultaneously, SARD will purchase the services of a Web monitoring and clipping service, such as CyberAlert, CyberScan, eWatch, or Webclipping. Results from the clipping services will be reviewed by SARD staff weekly. Even with a Web clipping service, SARD anticipates that it will be more fruitful to use its own staff to monitor chat rooms and discussion groups. A staff member will log into these groups two afternoons a week. If there are too many chat rooms and discussion groups to monitor in just two afternoons, SARD will randomly select the site(s) each login day. Staff will not interact with chatters unless there is a specific mention of street use of buprenorphine products or there appears to be indications of an adverse event. In those cases, SARD may chat for one session and only after clearly identifying itself and the project.

Passive Surveillance

There are additional sources of information that can indicate whether Subutex/Suboxone are implicated in abuse or fatalities. These sources will not provide the sort of real time and focused data that we can expect from the treatment program and street surveillance aspects of the project, but they can add to the picture.

Drug Abuse Warning Network (DAWN)

The federal Substance Abuse and Mental Health Administration's Office of Applied Studies (OAS) regularly publishes the results of its national sample of hospital emergency departments. The survey collects data on emergency department episodes that are related to the use of an illegal drug or the non-medical use of a legal drug. Coupled with the emergency department survey is the ongoing survey of 139 medical examiners in 40 metropolitan areas, which we will also use as a data source.

Community Epidemiology Work Group (CEWG)

SARD currently attends the CEWG meetings as an observer and it will continue to do so during the course of the project. The Federal Project Officer who oversees the activities of the CEWG, has agreed to encourage members to include the buprenorphine products in their local monitoring activities and to report on their findings at each meeting. The members will also be sent a letter explaining the study and given the 800 telephone number to call to report abuse or inappropriate use.

Other Surveillance Data Sources

Washington University in St. Louis will be conducting a post-marketing survey through a grant from Purdue Pharma, LP. Among other drugs that they will be monitoring is buprenorphine and OxyContin. Theodore Cicero, Ph.D., who is on the SARD Advisory Group, is the principal investigator of the Washington University study. Dr. Cicero has agreed to regularly provide the results of their findings on buprenorphine in exchange for SARD's findings on OxyContin, which is one of the drugs on SARD's *Product-Familiarity Interview*. Although the Washington University methodology is different from that proposed by SARD (polling of local experts knowledgeable of abuse patterns in their communities), the data they can provide would be useful in confirming SARD's findings.

Dr. Wilson Compton of the NIDA has agreed to send a letter to every NIDA grantee who has field workers interacting with drug abuse populations, requesting them to call the SARD 800 number if they learn of any abuse of Suboxone or Subutex in the course of their activities. If abuse of these products is reported, more intensive ethnographic studies will be conducted to verify the accuracy of the report and if accurate, the nature and extent of abuse of these products.

TESS is a staple of post-marketing surveillance. It is a system developed by the American Association of Poison Control Centers (AAPCC) to compile data from the U.S. poison centers. Its value derives from the fact that TESS collects data by brand name. TESS data will be monitored and included in periodic reports.

Drug Evaluation Network System (DENS)

DENS, a collaboration of the Treatment Research Institute at the University of Pennsylvania and the National Center on Addiction and Substance Abuse at Columbia University, is a relatively new national treatment-tracking project. Its goal is to provide current clinical and administrative information on patients entering into substance abuse treatment throughout the nation. Ultimately this system will include alcohol and drug treatment programs representatively sampled from all areas of the country. It focuses on the characteristics and severity of problems of patients entering into substance abuse treatment, their lengths of stay, and type of discharge. While a valuable tool for monitoring changes in the nation's substance abuse treatment population, a close examination of the types of drug use data that DENS collects leads us to doubt its relevance for post-marketing surveillance. In its current form the drug use categories are generic and do not permit identification of specific products.

Validation of the Methodology and Sample Size

Post-marketing surveillance of Suboxone and Subutex is being conducted for two purposes. The first purpose is to detect instances of abuse. These data may come from the reports from treatment programs or street ethnographers who are either part of SARD's active program or NIDA grantees who have been asked to contact the SARD 800 number. Such instances, if judged to be accurate by SARD and its Advisory Board, will result in two responses: increased surveillance to determine the nature and extent of abuse in that region; and notifying the sponsor who can take additional monitoring action in that region. The increased surveillance may take two forms: the recruitment of additional treatment programs and/or additional ethnographic studies in that region. In order to fulfill this first purpose, the post-marketing strategy proposed has been designed to be as widespread and accurate as possible. It should be noted that for this purpose it is not necessary to compare the rates of reports of instances of abuse with either the negative or positive control drugs included in this survey. All instances of abuse that are judged to be accurate will be pursued.

The second purpose of the post-marketing surveillance is to provide the Secretary of HHS with the data required by the DATA. Under this act, Schedule III, IV and V narcotic drugs approved for the indication may be prescribed by qualified physicians for the treatment of opiate dependence. The act further states that the Secretary of HHS must evaluate the impact of this program on increasing the availability of treatment for opiate dependent persons as well for any adverse public health consequences. Obviously for this purpose, data regarding the total number of people entering treatment for opiate dependence each quarter of the year as well as the number who are treated with Subutex or Suboxone are necessary. These data can then be used to determine the rate of reports of abuse in any quarter for every thousand prescriptions of Subutex and Suboxone. This rate will be compared to the rate of reports of abuse of our negative control drugs (Nardil, phenelzine, Elavil and amitriptyline). It is possible that the rates of reported abuse of Subutex and Suboxone will be greater than these negative controls that have little if any abuse

potential or actual street abuse. However, the most relevant comparison will be the rates of abuse of Subutex and Suboxone compared to methadone. The prescribing and dispensing of methadone is rigidly controlled in specially licensed treatment programs to prevent its illegal diversion. A comparison of the rates of abuse of methadone and Subutex and Suboxone to widely prescribed (and diverted) opiate medications (Vicodin, oxycodone, and OxyContin) will provide the Secretary of HHS with information that will aid in the decision as to the safety and effectiveness of Office-Based Treatment as provided for in the DATA.

In SARD's previous research using similar post-marketing surveillance techniques, it has been able to demonstrate that using treatment program interviews yields results that are consonant with a drug's known abuse potential. For example, phentermine, a drug with a low level of abuse as demonstrated by DAWN data, was reported to be abused on the street significantly more often by interviewees than a fictitious drug. This difference emerged in the first quarter of data collection when only 1,500 patients had been interviewed at 60 treatment sites. Therefore, SARD is confident that, with the sample size proposed in this project, it will be able to detect the appearance of the buprenorphine products listed in the *Product-Familiarity Interview* (Buprenex, Subutex, Suboxone) in the illegal market if it occurs.

Data Collection Instruments and Report Formats

Product Familiarity Interview

SARD has developed a one-sheet questionnaire (*Product-Familiarity Interview*) that will be incorporated within the regular information-gathering process that treatment programs use during intake of new clients. The *Interview* is designed to prevent the client from identifying the products that are the focus of the study. A copy of the questionnaire is included as attachment 3.

The interviews will be conducted with all persons being considered for admission to participating treatment programs. In addition to gathering basic demographic information (age, sex, race ethnicity, years of drug use, drug for which treatment is being requested), the *Product-Familiarity Interview* consists of questions dealing with the treatment applicants' familiarity with a list of drugs, knowledge of their street availability, and their personal knowledge of the use of the drugs. SARD expects that the average program will conduct up to nine interviews per month, which will yield approximately 29,000 over the 54 months that interviews will take place. The estimate of the probable number of interviews is based on the SAMHSA *Uniform Facility Data Set* and *Treatment Episode Data Set*, which reported 1,587,510 admissions in 15,239 substance abuse treatment facilities for the year 1999 (8.68 admissions/month). All questionnaires will be sent to SARD monthly and entered along with a 20% re-entered for quality control.

Adverse Events Information

The MedWatch *Adverse Events Information* form is to be used in the treatment programs at the time of intake. Interviewers will be instructed to: not describe any drug mentioned in the *Product-Familiarity Interview* beyond what is stated on this form; not answer questions about a

product; and not ask the participant any other questions about a product. However, if the participant spontaneously reports that he/she knows of someone who has had a drug reaction, developed a medical problem, or experienced some other adverse event that the participant believes was related to a drug product, the interviewer is to complete a MedWatch *Adverse Event Information* form.

Ethnographic Reports

Ethnographers will be asked to discuss the following topics in their reports. The topics are relatively standard for street ethnography.

Topics to be covered in street surveillance reports

1. Which types of drugs (Subutex/Suboxone) have you heard of from informants?
2. How did the informants acquire their drugs (prescription, friend, purchase on the street, etc.)?
3. Who primarily uses the drug (e.g. young people, women, Latinos, etc.)?
4. Which drug did informants use in the past 3 months?
5. Which drug did informants use to get high in the past 3 months?
6. Which drug did informants use more than once in the past 3 months?
7. How many informants have reported using these drugs in the past 3 months?
8. In what setting does each informant usually use the drug (home, party, club, etc.)?
9. Who do the informants usually use the drug with (male, female friends, lovers/partners, relatives, etc.)?

SARD has prepared a set of questions that ethnographers will be encouraged to use when interviewing their informants.

Guide for asking ethnographic questions about Subutex/Suboxone

1. Have you ever heard of:
   - Buprenorphine?
   - Subutex?
   - Suboxone?
2. When did you first hear about (Buprenorphine/Subutex/Suboxone)?
3. What did people tell you about it?
4. Have you ever tried (Buprenorphine/ Subutex/Suboxone)?
5. Before you tried (Buprenorphine/Subutex/Suboxone), what seemed appealing about it? What seemed unappealing about it?
6. In your impression, who uses (Buprenorphine/Subutex/Suboxone)?
7. Are (Buprenorphine/Subutex/Suboxone) users different from users of other drugs?
8. Have you heard references to (Buprenorphine/Subutex/Suboxone) in music, magazines, newspapers or movies; or on the radio, TV, or Web? If yes, tell me about it.
9. Tell me about the first time you tried (Buprenorphine/Subutex/Suboxone).
   a. How old were you?
   b. Where did you get the dose?
   c. Where were you?
   d. Who were you with? (probe: relations to these people, social networks, [etc.].)
10. Tell me about your use of (Buprenorphine/Subutex/Suboxone) since then.
    a. How frequently have you taken (Buprenorphine/Subutex/Suboxone)?
       i. Past month? How often?
       ii. Past year? How often?
       iii. More than a year ago?
       iv. Have you taken it regularly, or on-and-off?
    b. Tell me about the settings where you have taken (Buprenorphine/Subutex/Suboxone).
    c. Who have you taken (Buprenorphine/Subutex/Suboxone) with?

Materials and Methods Development

Attachment 4 presents a matrix that depicts the data collection plan. It maps instruments to data sources, respondents, focus, data collection tool, and data collection interval.

Approaches to Data Collection

At least for the first year of the project, data collection will be primarily through the use of paper-and-pencil forms. SARD has considered the possibility of using a Web-based data collection system, but has decided to put it temporarily on hold until it becomes more familiar with conditions in the field and the resources available to participants. Web based data collection would speed the availability of data from the field and expedite SARD's data analysis, but it may not be an improvement from the respondent's point of view. Treatment programs may not have computers in the areas where they conduct intake interviews. Ethnographers may find it disruptive to enter answers on a laptop or other portable device while conducting their interviews on the street. However, ethnographers may find a Web site as a convenient place to file their text-oriented quarterly and investigative reports. Because the sample of physicians constantly changes and training opportunities are minimal, data entry on a Web site would have to be extremely simple. SARD has the design and programming capability to develop a Web-based data collection system, if later warranted.

Development Schedule

A final draft of the *Product-Familiarity Interview* has been completed. An initial draft of an *Adverse Event Information* form can be found in Appendix 3. SARD must still develop an *Interviewer Packet*, which contains detailed instructions for intake interviewers at the treatment programs. It will be developed in the first month of the project. Also in the first month, SARD will develop:

- Letters, to be sent before telephone contact, inviting treatment programs and physicians to participate in the project;
- Brief survey form, which will accompany the invitation letters, that programs and physicians will complete describing their programs/practices (types of populations served, admissions/patients per year, etc.);
- *Agreement to Participate* for programs, physicians, and ethnographers to sign, which describes conditions for participation, mutual responsibilities, SARD's method of payment, data ownership, etc.; and
- Packet containing materials that participants may wish to use, if they plan to seek approval of their local Institutional Review Boards (IRB).

In the second month, SARD will finalize information collection guidelines and reporting protocols for the ethnographers. By the end of the second month SARD expects to have all materials completed.

SARD anticipates that the third month will be spent preparing for and awaiting IRB approval. All materials will be provided to the FDA before SARD goes into the field in the fourth month.

Roles in Post Marketing Surveillance

SARD will be responsible for the design and implementation of all data collection activities described in this document and summarized in Appendix 4. SARD will identify and recruit treatment programs and ethnographers. It will also recruit physicians using lists provided by CSAT and the sponsor. SARD will:

- Maintain ongoing liaison with participants;
- Conduct training, monitor compliance with data collection protocols;
- Staff a help desk to answer inquiries from the field;
- Receive the data from the field;
- Reimburse respondents for their participation;
- Enter and clean data and maintain the database;
- Conduct the data analyses;
- Summarize findings;
- Institute ethnographic investigations;
- Convene the Advisory Group and serve as its secretariat; and
- Prepare reports for the sponsor.

The sponsor will be responsible for all FDA regulatory and reporting requirements.

Reports

The sponsor will receive two types of reports from SARD's post-marketing surveillance project. The first will deal with indicators of buprenorphine abuse and the second with adverse events.

Emerging Patterns of Abuse

SARD will report patterns of abuse findings to the sponsor on a quarterly basis. These reports will include data for the last quarter as well as cumulatively from the patient interviews at the treatment programs. In addition the reports by the ethnographers as well as a summary of spontaneous calls alleging the abuse of Suboxone or Subutex to the SARD 800 number will be provided. The reports also will be sent to an Advisory Group of nine substance abuse experts, who will be asked whether they believe that the report indicates that a pattern of Subutex/Suboxone abuse is emerging in any region of the country that warrants alerting the

FDA. If indicated, the Advisory Group will be convened for either a face-to-face meeting or telephone conference call to deliberate in conjunction with the sponsor on what actions should be taken to curb further instances of diversion and abuse. A meeting of the Advisory Group will automatically be convened to prepare an opinion for the sponsor on the possible emergence of buprenorphine as a drug of abuse whenever any of the following conditions occur:

- At least three of the Advisory Group members suggest that a meeting is warranted because of the confluence of surveillance findings;
- An ethnographer has followed up on the death of a buprenorphine user and found that the person had no previous history of opiate abuse or that there is sufficient reason to believe that buprenorphine caused or contributed to the death;
- Reports by any ethnographer that a street trade in buprenorphine products is apparent in their communities;
- More than 10 calls reporting the abuse of Subutex or Suboxone are received on the SARD 800 number in any quarter from different individuals in the same region of the country;

As soon as it becomes apparent that one of these conditions exists, the sponsor will immediately be notified, even before the Advisory Group has had an opportunity to discuss the occurrence.

Adverse Events

SARD will report all serious "adverse events" that fall within FDA criteria to the sponsor within one working day of first becoming aware of the event. The following criteria will be used to determine when a report from the field will be considered an adverse event:

- There is a specifically identifiable adverse event;
- At least one demographic factor (age, sex, initials) is known about the person who experienced the adverse event; and
- The reporter (who may have only second hand knowledge of the event) attributes the adverse event to Suboxone or Subutex.

This definition of an adverse event will guide all decisions as to when an event is considered sufficiently serious to require reporting. A serious adverse event is any event that is:

- Fatal;
- Life-threatening (life-threatening is defined as the person was at immediate risk of death from the adverse event as it occurred);
- Significantly or permanently disabling;
- Serious enough to require in-patient hospitalization, or that prolongs hospitalization; or

- A congenital anomaly or birth defect.

An important medical event that may not result in death, be life-threatening, or require hospitalization will be considered a serious adverse drug experience when, based upon appropriate medical judgment, it may jeopardize the person and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

We also consider the development of drug dependency or drug abuse as a reportable adverse event. If we become aware of a specific case of abuse in a person with no previous history of opiate abuse and we have at least one demographic factor, we will treat it as an adverse event and report it to the FDA within 15 days.

Significant events including new addictions, reports of abuse of buprenorphine in opioid naive individuals, death due to overdose, and neonatal withdrawal will be reported to the FDA as 15-day safety reports.

Advisory Group

Following is a list of the individuals who have agreed to serve on the Advisory Group. SARD believes that they provide the diversity of backgrounds necessary to monitor changing patterns of drug use.

James C. Anthony, Ph.D.
Professor of Epidemiology
Johns Hopkins School of Public Health

Warren Bickel, Ph.D.
Professor and Interim Chair
Department of Psychiatry
University of Vermont School of Medicine

Carol Boyd, RN., Ph.D.
Professor and Director
Substance Abuse Research Center
University of Michigan

Morton B. Brown, Ph.D.
Professor of Biostatistics
School of Public Health
University of Michigan

Thomas Crowley, M.D.
Professor of Psychiatry
University of Colorado
School of Medicine

Margaret E. Ensminger, Ph.D.
Professor and Associate Chair
Dept. of Health Policy and Management
Johns Hopkins School of Public Health

Charles P. O'Brien, M.D., Ph.D.
Kenneth Appell Professor of Psychiatry
University of Pennsylvania

Richard Schottenfeld, M.D.
Professor of Psychiatry
School of Medicine
Yale University

Theodore Cicero, Ph.D.
Vice Chancellor for Research
Washington University

Training and Monitoring Respondents

Treatment Programs

Each participating treatment program will designate an individual to serve as the site's Post Marketing Coordinator (PMC) who will be responsible for collecting data at that site in an accurate and consistent manner. These individuals will receive training in the following manner. First, all forms to be used for data collection at the site, along with complete instructions, will be sent to the PMCs. When they have confirmed by phone that they have received these materials, a teleconference call will be scheduled to go over the instructions and to answer any questions they may have regarding the manner in which the forms are to be used. They will then be asked to administer the forms to 10 patients already enrolled in their program over the next week and to send copies of these forms to SARD. After these have been received by SARD a second teleconference call will be scheduled to go over any questions that may have arisen during the test run. After the SARD trainer is satisfied that the individual understands the manner in which the forms are to be used, they will be instructed to begin collecting data on new clients. If the PMC becomes unavailable for these duties, no data will be collected until a new PMC is trained as described above.

SARD will establish an 800 number, which will be given to each of the treatment programs. SARD staff will take calls from PMCs from 8:30 AM to 5:00 PM EST Monday through Friday and answer any questions regarding the data collection forms or procedures. At other hours a voice mail system for recording queries will be operative. These queries will be answered as early as possible on the next working day. If there is a question regarding the accuracy of the data collected during an intake interview, the form will be marked by the PMC so that it will not be included in the database.

On a monthly basis, SARD will contact each PMC to determine whether any problems have been encountered during data collection. Again, if the SARD staff detects that the treatment program is having difficulty collecting data in a consistent manner, the data from that program will not be used until the problems have been corrected. Programs that continue to have data collection problems will be dropped from the project and their data flagged as questionable in the database.

Ethnographers

Most of the ethnographers to be used in this project are individuals with a long history of NIDA funded grants. Dr. Carol Boyd (Professor of Anthropology and Director of the University of Michigan Substance Abuse Research Center) will supervise their work and be responsible for instructing them in their data collection efforts. After they have received the questions they will ask their street informants, Dr. Boyd will arrange a teleconference call with all 10 of the ethnographers to discuss the program, and the data to be collected and reported to SARD. Data collection will begin after Dr. Boyd judges that these individuals completely understand the nature of the program, the data that are to be collected, and the reporting requirements. There will be monthly teleconference calls with the ethnographers to discuss findings. Dr. Boyd will summarize these conference calls for inclusion in our quarterly report to the sponsor. If any of the ethnographers detect the street sale or abuse of Subutex or Suboxone, they will immediately report this to SARD. This information will be immediately transmitted to the sponsor.

This surveillance project will be ready for implementation before approval and will be implemented at the time of product approval and continued for the first five years of marketing of Subutex/Suboxone and will be reviewed at the end of three years, with an analysis of the effectiveness of this program in detecting serious trends in abuse of this product submitted to the FDA.

SARD plans to be in the field (treatment programs and ethnographers) collecting data, within 60 days of initial distribution. The first analytic report will be sent to the company by the end of the seventh month, unless more frequent reporting is required. No interviews will be conducted in the last month of the project, which will be dedicated to writing a final report.

PROFESSIONAL EDUCATION

An educational package to include information about appropriate prescription management and safeguards will be mailed to those physicians qualified under the Drug Addiction Treatment Act of 2000. This package will include a "notification form" (included in physician brochure text at attachment 5) which will allow the physician to provide all information required by the Act for submission to the Secretary (CSAT) as well as a product monograph, which is currently in development and will be submitted to the Division of Drug Marketing, Advertising and Communications prior to use. Information for Patients (Included at Attachment 6), and a physician brochure – *Answers to Frequently Asked Questions* (Included at Attachment 5) will be included in the package. The development of a patient/family video is being considered to aid physicians in instructing patients and their families regarding appropriate use. This information will also be provided to members of pertinent medical associations such as the American Society of Addiction Medicine, the American Academy of Addiction Psychiatry and the American Psychiatric Association. These educational kits will additionally be available through sales representatives and at medical conventions.

Physicians will be encouraged at the outset of treatment to prescribe no more than one week of treatment initially. Physicians will be encouraged to monitor patient treatment progress via urine testing. Furthermore, when Subutex is used for induction, physicians are encouraged to switch patients onto Suboxone as soon as possible. Educational materials for physicians will be mailed to all qualified physicians who have notified the Secretary of their intention to use Suboxone/Subutex products. These materials will also be available on our web site or via the Call Center upon request. Additionally the Sales Representatives will have all materials to distribute to appropriate recipients. Patient Guides will also be made available through these same procedures. Pharmacist Guides/Educational Brochures (Attachment 7) will be mailed to Pharmacists via an existing internal Pharmacists Response Network which is an interactive database / communication service to member pharmacists. Pharmacist Educational materials will also be made available via Sales Representatives. The highly trained sales representatives will assist us in determining whether the Educational messages have been received/implemented and will be able to provide further information to educational recipients based on this training.

Educational symposia will be funded at national pharmacist association meetings to discuss the new treatment paradigm and associated risks. Product information and safeguards against diversion will also be highlighted in an American Pharmaceutical Association communication sent to pharmacies nationally.

The company will cooperate with DEA in providing pharmacies with access to information that will allow them to determine that a physician is qualified to prescribe Subutex and Suboxone by establishing a web site (www.suboxone.com) and a toll-free (1-877 SUBOXONE) (1-877-782-6966) number for pharmacists to verify that a given DEA registration number is qualified to

prescribe Subutex and Suboxone. This web site will also be useful as a referral source to qualified physicians.

DECISION POINTS IN DISTRIBUTION SYSTEM RE: DIVERSION

Physician Request

1) Physicians will be provided educational materials, as described in the risk management document, which include ordering instructions and a toll free number to order product.

2) Physicians will be given an option to order drug directly from a wholesaler or through a local pharmacy rather than having a patient fill prescriptions through local pharmacies.

3) The Drug Addiction Treatment Act requires that physicians be qualified prior to writing Subutex or Suboxone prescriptions for the treatment of opiate dependence

4) In the form of educational materials, guidelines will be given to wholesalers referencing certification requirements of physicians prior to prescribing.

5) Part of all wholesalers' standard operating procedures includes suspicious order monitoring. Benchmark recommendations will be provided to wholesaler.

Decision Point: Physicians

- Physician has proper credentials (verify DEA Registration number, name, address, schedule and expiration date of the DEA Registration; or request a copy of completed CSAT notification form for file) – Fill Order

- Physician does not have proper credentials – Deny Order; Send educational materials to physician describing physician qualification requirements.

6) Part of all wholesalers' standard operating procedures includes suspicious order monitoring. Benchmark recommendations will be provided to wholesaler.

Decision Point:

- Request meets order quantity guidelines – Fill Order

- Request exceeds order quantity guidelines – Review order, contact physician, document action taken. If warranted, report to DEA.

7) Wholesaler purchases of Subutex/Suboxone from distribution facility

Decision Point:

- Request meets order quantity guidelines – Fill Order

- Request exceeds order quantity guidelines – Review order, contact wholesaler, document action taken. If warranted, report to DEA.

8) We will report documented suspicious orders to DEA as they occur.

Wholesaler/Pharmacy

9) Educational materials referring to DATA will be provided to pharmacies

10) Patient will present prescription to pharmacy

11) Pharmacy will order product through normal wholesaler channels based on patient demand.

Decision Point:

- Request meets order quantity guidelines – Fill Order
- Request exceeds order quantity guidelines – Review order, contact pharmacy, document action taken. If warranted, report to DEA.

12) Wholesaler adheres to ARCOS tracking system as required by law

13) Pharmacy will fill prescription after verifying that physician has proper credentials to write Subutex or Suboxone prescription. Overview of DATA will be provided via education plan to pharmacists.

Decision Point:

- Through educational materials sent to pharmacists, through APhA communications and from the company sponsored mailings, we will recommend that pharmacists determine that physicians are properly qualified prior to filling prescriptions.
- Physician has proper credentials – Fill Order
- Physician does not have proper credentials – Deny Order; Send educational materials to physician describing physician certification requirements

14) Wholesaler requests Subutex/Suboxone from distribution center

Decision Point:

- Request meets order quantity guidelines – Fill Order
- Request exceeds order quantity guidelines – Review order, contact wholesaler, document action taken. If warranted, report to DEA.

15) We will report documented suspicious orders to DEA as they occur.

Decision Points in Surveillance System re: Diversion

When a pattern of abuse or diversion is uncovered by SARD, the Advisory Group and the local ethnographer will be convened for either a face-to-face meeting or telephone conference call to deliberate, in conjunction with the sponsor and FDA, on what actions could be taken to curb further instances of diversion and abuse. The Advisory Group, with the advice of the local ethnographer, will be expected to suggest interventions that are tailored to the specific community where abuse/diversion has been found.

Attachment 1:

Call Center Script – Phase 1

SUBOXONE Call Center Script — Phase I

Physicians

PROMPT **For a brief description of SUBOXONE and SUBUTEX, press 1.**

COPY SUBOXONE and SUBUTEX are 2 new drugs recently approved for the treatment of opioid dependence. They are the first such therapies to be approved for office-based treatment under the Drug Addiction Treatment Act of 2000.

SUBOXONE combines buprenorphine, a partial opioid agonist, with naloxone, an opioid antagonist, in a sublingual tablet. SUBUTEX is buprenorphine without the naloxone. For a more detailed description of these medications, please visit our Web site at www.suboxone.com.

PROMPT **There are certain steps physicians must take before prescribing SUBOXONE and SUBUTEX. To learn more, press 2.**

COPY In accordance with the Drug Addiction Treatment Act of 2000, physicians must notify the Secretary of Health and Human Services, and meet certain qualifications, before prescribing SUBOXONE or SUBUTEX. You can review these qualifications and download a notification form from our Web site at www.suboxone.com.

PROMPT **For availability and distribution of SUBOXONE and SUBUTEX, press 3.**

COPY SUBOXONE and SUBUTEX will be available through your pharmacy within several months. To ensure patients' access, you may want to establish relationships with more than one pharmacy carrying these products.

Most physicians will want to keep supplies of medication in their offices for initiating treatment under direct supervision. To order SUBOXONE or SUBUTEX directly, press ((X)) to reach a customer service representative. Alternately, you can get SUBOXONE or SUBUTEX from your routine supplier of vaccines and injectable products. If you do not have a supplier relationship established, contact us and we will help you arrange one. Log on to www.suboxone.com to learn more.

PROMPT **For all other questions or issues, press 4.**

COPY To learn more about treating patients with SUBOXONE or SUBUTEX, please log on to our Web site at www.suboxone.com. To speak with a representative, press ((X)). Or, to receive more information by phone or mail, press ((X)) to leave us your name, phone number, and address.

Pharmacists

PROMPT **For a brief description of SUBOXONE and SUBUTEX, press 1.**

COPY SUBOXONE and SUBUTEX are 2 new drugs recently approved for the treatment of opioid dependence. They are the first such therapies to be approved for office-based treatment under the Drug Addiction Treatment Act of 2000.

SUBOXONE combines buprenorphine, a partial opioid agonist, with naloxone, an opioid antagonist, in a sublingual tablet. SUBUTEX is buprenorphine without the naloxone. For a more detailed description of these medications, please visit our Web site at www.suboxone.com.

PROMPT **To learn who is qualified to prescribe SUBOXONE and SUBUTEX, press 2.**

COPY The Drug Addiction Treatment Act of 2000 allows for office-based prescribing of SUBOXONE and SUBUTEX by qualified physicians. Physicians who meet the qualification criteria must notify the Secretary of Health and Human Services of their intent to prescribe SUBOXONE ansd SUBUTEX for opiate dependence, and will have a unique identification number issued by the Drug Enforcement Agency

However, because it can take up to 45 days for their application to be reviewed, in emergency situations, physicians can begin prescribing SUBOXONE or SUBUTEX before they have received a special DEA identification number. If you have any questions about the validity of a prescription, contact the physician for clarification.

More information on physician qualification is available through our Web site at www.suboxone.com. You can also determine if a particular physician has made the appropriate notification by calling 1-866-BUP-CSAT.

PROMPT **For availability and distribution of SUBOXONE and SUBUTEX, press 3.**

COPY SUBOXONE and SUBUTEX will be available for commercial distribution within several months. You can order them through your regular drug wholesaler.

PROMPT **For all other questions or issues, press 4.**

COPY To learn more about treating patients with SUBOXONE or SUBUTEX, please log on to our Web site at www.suboxone.com. To speak with a representative, press ((X)). Or, to receive more information by phone or mail, press ((X)) to leave us your name, phone number, and address.

Patients

PROMPT **Your desire for privacy is important to us. To hear our confidentiality statement, press 1.**

COPY We understand that seeking treatment for drug addiction is an extremely personal matter. That's why we've designed this help line to be completely confidential. If you choose to leave your name, phone number, or address as part of a request for more information, please be assured that we will hold this in strict confidence, and use it only for the purposes of fulfilling your specific request.

PROMPT **For a brief description of SUBOXONE and SUBUTEX, press 2.**

COPY

SUBOXONE and SUBUTEX are 2 new medications used to treat opioid dependence. **These are first drugs of this kind that can be given to you by a regular doctor, in a doctor's office, meaning that once stabilized you will not have to go to a special clinic every day to get treatment.**. Qualified doctors can give you SUBOXONE or SUBUTEX right in the office, and, depending on how you are doing in treatment, your doctor may even give you a prescription so you can take your medication in the privacy of your home. To learn more about SUBOXONE, SUBUTEX, and treatment for opioid dependence, visit our Web site at www.Suboxone.com

PROMPT

To get more information on SUBOXONE or SUBUTEX, press 3.

COPY

For more information on treating opioid addiction with SUBOXONE or SUBUTEX, visit our Web site at www.suboxone.com.

If you have a specific question you'd like answered, press ((X)) to leave us a message. If you'd prefer a response by phone, be sure to include your phone number, best time to call, and, if you wish, your name. Let us know if it is o.k. to leave a message on your answering machine, or if you'd prefer we not do so. To receive additional information by mail, please leave your name and address. We will hold any personal information you give us in strict confidence, and use it only for the purposes of fulfilling your specific request.

Note: All callers will have the option of pressing (X) to be transferred to call center staff for personal contact

Attachment 2

Pool of Individuals For Provision of Ethnographic Services

Ethnographers and community outreach workers

City/State	Contact	Affiliation	Type
Atlanta, GA	Claire Sterk, Ph.D.*	Emory University	C
	Sandra S. McDonald	Health Outreach Project, Inc.	O
Austin, TX	Jane C. Maxwell, Ph.D.*	University of Texas at Austin	C
Baltimore, MD	Leigh Henderson, Ph.D.		C
	Indira Kotval	Health Education Resource Organization	O
	Eric Wish	Center for Substance Abuse Research, University of Maryland	
Bridgeport, CT	Susan Chudwick	Greater Bridgeport AIDS Prevention Project	O
New York, NY	Carlos Allende	Vocational Instruction Project	O
Boston, MA	Thomas W. Clark	Health and Addictions Research, Inc.	C
Chicago, IL	Lawrence Ouellet, Ph.D.*	Community Outreach and Intervention Projects	C
	Tonda Hughes	University of Illinois, Chicago	
Detroit, MI	Luke Bergmann	University of Michigan	
	Dan Rosen	University of Michigan	
Honolulu, HI	D. William Wood, Ph.D.	Department of Sociology University of Hawaii	C
	Meda Chesney-Lind		
Los Angeles, CA	Beth A. Finnerty, MPH	UCLA Integrated Substance Abuse Program	C
Deleware	James Inciardi	University of Deleware	

Ethnographers and community outreach workers

Miami, FL	James N. Hall	Up Front Drug Information Center	C
Minneapolis, MN	Carol Falkowski	Butler Center for Research	C
Nashville, TN	Sharon Crawford.	Metro Interdenominational Church	O
New Orleans, LA	Kathleen Boyle		
	Gail Thorton Collins		
New York, NY	Carlos Allende	Vocational Instruction Project	O
	Phillipe Burgois		
	Eloise Dunlap	National Development and Research Institutes	
	Bruce Johnson	National Development and Research Institutes	
Ohio	Bob Carlson		

* Contacted and agreed to participate
C = member of CEWG; O = CSAT funded street outreach program

City/State	Contact	Affiliation	Type
Phoenix, AZ	Ilene Dode, Ph.D.	Empact-Suicide Prevention Center, Inc.	C
San Francisco, CA	John Newmeyer, Ph.D.	Haight-Ashbury Free Clinics, Inc.	C
	Brian R. Edlin	University of California at San Francisco	O
St. Louis, MO	Heidi Israel	Division of Infectious Diseases, St. Louis University School of Medicine	C
St. Petersburg, FL	Patrick Hughes, M.D.		
	Tom Mieczkowski	University of South Florida	
Tampa, FL	Wilson Palacio		
Washington, DC	Angela Fulwood	Family and Medical Counseling Services, Inc.	O

* Contacted and agreed to participate
C = member of CEWG; O = CSAT funded street outreach program

Attachment 3

Product-Familiarity Interview

Product Familiarity

INTERVIEWER INSTRUCTIONS

Side One: Complete this side of the form first. You should be able to complete the participant information on this side from the admission information that you have already collected.

Side Two: After reading the instructions to the participant, read the question at the top of each the column. After reading a question, read down the list of products in the first column. If the participant says he/she is not familiar with a product the first time, leave it off the list of products when you ask the remaining questions. Do not describe a product beyond what is stated on this form and do not answer questions about a product. Do not ask the participant any other questions about a product. However, if the participant spontaneously reports that he/she knows of someone who has had a drug reaction, developed a medical problem, or experienced some other adverse event that the participant believes was related to a drug product, complete an *Adverse Event Form*, which is found in your *Interviewer Packet*.

Definitions

Interview Location: See your guidebook.
Date: Date of the interview.
Staff ID: First and last initial, and last four digits of interviewers Social Security Number.
Race: If a participant refuses to accept any of the racial categories, leave them all blank.
Nonprescription methadone: Only mark this item, if the participant is using a substance abuse treatment medication without a prescription or is using it in a manner that was not prescribed. Only consider psychoactive medications
Primary drug of abuse: Use your program's own definition of "primary drug of abuse."
Years using primary drug of abuse: Begin with the year first used, not necessarily the first time used to get high

Interview Location ☐☐☐☐

Date ☐☐☐☐☐☐ Staff ID ☐☐☐☐☐☐

PARTICIPANT INFORMATION

Sex
- Male ☐
- Female ☐

Hispanic
- No ☐
- Yes ☐

Race (Mark all that apply)
- American Indian or Alaska Native ☐
- Asian ☐
- Black or African American ☐
- Native Hawaiian/Other Pacific Islander ☐
- White ☐

(Specify)

Age ☐☐

Primary drug of abuse (Mark only one)
- Alcohol ☐
- Marijuana/hashish
- Cocaine/crack ☐
- Heroin or other opiates ☐
- Nonprescription methadone, LAAM, or other medication used for treating ☐
- Hallucinogens (PCP, LSD, mescaline) ☐
- Methamphetamine or other stimulants ☐
- Benzodiazepines, barbiturates, tranquilizers ☐
- MDMA (Ecstasy) ☐
- Inhalants (glue, poppers, rush) ☐
- Other ☐

(Specify)

Years using primary drug of abuse ☐☐

Subutex/Suboxone Surveillance

PARTICIPANT INSTRUCTIONS

We are cooperating in a national research project that is trying to determine how familiar people, who come to treatment programs, are with different drugs and medications. I'd like to ask you to participate. It will only take a couple of minutes. None of the information that I will collect will identify you in any way. If you don't want to participate, you don't have to – we'll just rip up this form. If you refuse, it won't affect the services you will receive from us.

I am going to read you a list of drugs and medications that you might know about. For each product that I name, I would like you to tell me if you ever heard of it. Then I will ask you whether you or someone you know used any of the products, and whether you or someone you know ever used the product to get high. Finally, I'll want you to tell me whether you think that the product is sold on the street. (Do one column at a time. Only repeat a product name, if participant heard of it.)

	1 Which of these products have you heard of?	2 Which of these have you, or someone you know, used in the past 3 months?	3 Which of these have you, or someone you know, used to get high in the past 3 months?	4 Which of these have you, or someone you know, used more than once to get high?	5 Which of these have you seen or heard of being sold on the street in the past 3 months?
Oxycontin	Y N	Y N	Y N	Y N	Y N
Elavil	Y N	Y N	Y N	Y N	Y N
Methadose	Y N	Y N	Y N	Y N	Y N
Oxycodone	Y N	Y N	Y N	Y N	Y N
Vicodin	Y N	Y N	Y N	Y N	Y N
Buprenex	Y N	Y N	Y N	Y N	Y N
Subutex	Y N	Y N	Y N	Y N	Y N
Nardil	Y N	Y N	Y N	Y N	Y N
Methadone	Y N	Y N	Y N	Y N	Y N
Buprenorphine	Y N	Y N	Y N	Y N	Y N
Amitryptaline	Y N	Y N	Y N	Y N	Y N
Dolophine	Y N	Y N	Y N	Y N	Y N
Suboxone	Y N	Y N	Y N	Y N	Y N
Phenobzine	Y N	Y N	Y N	Y N	Y N

Attachment 4

Matrix of Data and Information Sources

Source/Item	Respondent	Focus	Collection Tool	Interval
Treatment Programs				
CTN Provider List Geographic location	NIDA CTN Project Officer	Treatment programs	List	Before polling programs for interest in participating
Substance Abuse Treatment Locator Web Site Geographic location Services provided	Web site	Treatment programs	List of programs by geographic location	Before polling programs for interest in participating
Product-Familiarity Interview (PFI) Sex Hispanic Race Age Primary drug of abuse Years using primary drug of abuse? Which of these drugs: • Have you heard of… • Have you, or someone you know, ever used… • Have you, or someone you know, ever used to get high… • Which of these do you think is sold on the street…	Treatment Admissions	Familiarity with Subutex/Suboxone and other products and their use on the street. The products are: OxyContin Elavil Methadose Oxycodone Vicodin Buprenex Subutex Amitriptyline Methadone Buprenorphine Nardil Dolophine Suboxone Phenelzine	Structured interview by intake worker of all treatment program admissions	Continuous. PFI forms sent to SARD monthly
Adverse Event Information	Treatment admissions spontaneously mentioning that they know of an adverse buprenorphine event	Identify serious adverse events	Structured interview conducted by intake worker at treatment program who fills out standardized form	Forms sent in immediately upon completion
Physicians				
Physician's Reporting Form (PRF)	Addiction medicine physicians	Illicit buprenorphine use by patients and their knowledge of street use	Open ended questions on structured form	Monthly polling of 10% sample of physicians
Ethnographers				
Product-Familiarity Interview (optional)	Street users	Familiarity with Subutex/Suboxone and other products and their use on the street	Structured interview by ethnographers of key/other informants	50/ethnographer repeated quarterly
Street Surveillance Reports Which types of drugs (Subutex/Suboxone) have you heard of from informants How did the informants acquire their drugs (prescription, friend, purchase on the street, etc.) Who primarily uses the drug	Ethnographers	Presence of buprenorphine on street and patterns of use	Informal interview guided by SARD suggested questions	Quarterly ethnographic reports

Source/Item	Respondent	Focus	Collection Tool	Interval
(e.g. young people, women, Latinos, etc.) Which drug did informants use in the past 3 months Which drug did informants use to get high in the past 3 months use Which drug did informants use more than once in the past 3 months How many informants have reported using these drugs in the past 3 months? In what setting does each informant usually use the drug (home, party, club, etc.) Who do the informants usually use the drug with (male friends, female friends, lovers/partners, relatives, etc.)				
Ethnographic Investigations	Health, law enforcement, and other local informants	Track down emerging buprenorphine abuse, define patterns of use and market dynamics	Informal interviews, examination of available documents, and other fact finding	Conduct investigation: On the death of a buprenorphine user with no previous history of opiate abuse or when there is sufficient reason to believe that buprenorphine caused or contributed to the death; Ethnographer suspects that a street trade in buprenorphine products is emerging; A local treatment program finds that 5% of admissions report nonprescription use of buprenorphine; A local physician expresses a suspicion that buprenorphine products are being abused based on patient reports.
Media Surveillance				
Web Monitoring	Drug related Web sites and chat room participants	Determine attitudes about buprenorphine, especially its value in getting high or managing a habit		Surf drug Web sites 2 days a week for 4 hours
News Clipping Services	News media	Identify localities where buprenorphine is viewed by officials or the general public as problematic	News articles	Reviewed weekly by SARD
Community Epidemiology Work Group (CEWG)				
CEWG Meetings	Ethnographer members of CEWG	Identify national patterns of buprenorphine abuse	Group discussion	Semiannual meetings
Other Surveillance Data Sources				
Washington University/Purdue Pharma	Local drug abuse experts	Determine rates of abuse, addiction, misuse, diversion of seven drug types including buprenorphine and OxyContin	Self-administered questionnaire	Quarterly

Physician Information

Answers to Frequently Asked Questions

Who is qualified to prescribe SUBOXONE or SUBUTEX?

Physicians who:

- Meet one or more of the following training requirements
  - Hold a subspecialty board certification in addiction psychiatry from the American Board of medical Specialties
  - Hold an addiction certification from the American Society of Addiction Medicine
  - Hold a subspecialty board certification in Addiction Medicine from the American Osteopathic Association
  - Have completed not less than 8 hours of authorized training on the treatment or management of opioid-dependent patients. This training may include classroom situations, seminars at professional society meetings, electronic communications, or other media. The American Society of Addiction Medicine, The American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association, and the American Psychiatric Association are all authorized to provide this training. Details and website addresses can be found in the section below.
- AND meet both of the following criteria:
  - Have the capacity to provide or to refer patients for necessary ancillary services, such as psychosocial therapy.
  - Agree to treat no more than 30 patients at any one time in their individual or group practice

When and where are training sessions being held?

Each of the above organizations has scheduled training sessions. You may contact them directly at the addresses below, or visit their web sites. Additionally, you can call the toll-free SUBOXONE help line at 1-877-SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com.

The American Academy of Addiction Psychiatry
7301 Mission Road, Suite 252
Prairie Village, KS 66208
Telephone: (913) 262-6161
E-mail: info@aaap.org
Web site: www.aaap.org

The American Society of Addiction Medicine

4601 North Park Ave. Arcade Suite 101
Chevy Chase, MD 20815
Telephone (301) 656-3920
E-mail: email@asam.org
Web site http://asam.org

The American Psychiatric Association
1400 K Street N.W.
Washington, DC 20005
Telephone (888) 357-7924
E-mail: apa@psych.org
Web site: http://www.psych.org

American Osteopathic Association
142 East Ontario Street
Chicago, IL 60611
Telephone (800) 621-1773
E-mail: info@aoa-net.org
Web site: http://www.aoa-net.org/

I am already qualified. What do I do next?

The Drug Addiction Treatment Act (DATA) requires that before you begin prescribing SUBOXONE or SUBUTEX you must notify the Secretary of Health and Human Services of your intent to treat patients with these products. The agency within the Department of Health and Human Services to be notified is the Substance Abuse and Mental Health Services Administration (SAMHSA). Notification is handled within SAMHSA by the Division of Pharmacologic Therapies (DPT) within the Center for Substance Abuse Treatment (CSAT). For convenience CSAT has developed a form that may be used for your notification. A copy is enclosed in this package
You may complete the notification form online or download the form by visiting CSAT's web site at www.dpt.samhsa.gov. The form may also be downloaded from www.suboxone.com. If you prefer, you may also notify by letter if you include all of the required information.
All forms (or letters) should be mailed or faxed to:

Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
Division of Pharmacologic Therapies
Attn. Opioid Treatment Waiver Program
5600 Fishers Lane, Rm. 12-105
Rockville, MD 20857
FAX: (301) 443-3994

Call CSAT/DPT if you have any questions about the notification process or need help completing the form. They can be reached at (301) 443-7745.

What happens after my notification is sent to CSAT?

CSAT will communicate with the Drug Enforcement Administration (DEA), review your notification and then notify DEA that you are qualified as required by the DATA. The DATA allows 45 days for this review process. No later than at the end of that 45-day period, DEA will issue a unique identification number indicating that you are a qualifying physician under the DATA. DEA is developing regulations that will require this number along with your existing DEA registration number to be included on all prescriptions issued for the treatment of opioid dependence under the DATA; therefore it is strongly recommended that you include this number when you write prescriptions for Subutex and Suboxone for the treatment of opioid dependence. CSAT will send you a letter notifying you of the new DEA identification number that will be assigned. You will subsequently receive a revised DEA registration certificate (showing both numbers).

Do I have to wait 45 days before treating patients?

The DATA envisions physicians notifying CSAT as soon as they are qualified, but makes provision for those who find themselves in the position of being qualified and needing to treat a patient, but not having notified CSAT In this case, you must first notify CSAT and DEA of your intent before treating the patient; this can be done electronically on the internet by checking the appropriate box, or by faxing in the form included in this package to CSAT at: (301) 443-3994

During the training sessions, as well as in the product information and CSAT Guidelines, it is recommended that patients be given initial doses under supervision. It is not my normal practice to keep a stock of controlled substances in my office. How do I get SUBOXONE or SUBUTEX for use in the office?

State laws vary regarding stocking of controlled substances. Information on State requirements can be found on our website, If you have a routine supplier of products such as vaccines, or injectable products that you use in your office, that supplier will be able to provide you with SUBOXONE and SUBUTEX. If you do not have a normal supplier of such products we will facilitate the establishment of a relationship with a supplier. Please complete the enclosed pre-addressed request form and mail it to us. Alternately, you may call our toll-free SUBOXONE Help Line at 1 877 SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com. In those States where permitted, we will provide you with an initial supply of SUBOXONE or SUBUTEX for induction use.

What storage and record-keeping requirements are associated with maintenance of a supply of SUBOXONE and SUBUTEX in my office?

For a full listing of requirements for a specific State you may call our toll-free SUBOXONE Help Line at 1 877 SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com. Generally, you will be required to keep

the medications in a secure environment. They should be kept in a locked compartment with limited access. You will also be required to maintain a written record of the disposition of all doses. Usually this can be done with the maintenance of a logbook in which you record all incoming doses and account for each dispensed dose as it is used. This record must be kept current at all times. Additional requirements may be in place in your State.

While I appreciate the convenience of maintaining a supply of SUBOXONE and SUBUTEX in my office for induction purposes, the situation at our office precludes such an arrangement. How to I manage supervised induction doses without maintaining such a supply in my office?

For those physicians who do not wish to maintain a supply of SUBOXONE or SUBUTEX in their offices, where State law and regulation allows, we will provide coupons for you to provide to your patient for their initial doses. In this circumstance, you would write a prescription only for the initial dose of SUBOXONE or SUBUTEX. If pharmacy delivery services are available, you may choose to arrange to have the dose delivered to your office; if not give the prescription, and a coupon, to the patient (or, if available, to a trustworthy family member accompanying the patient) with instructions that the prescription is to be taken to the pharmacy, filled, and brought back to your office for dosing. It is recommended that you call or fax ahead to ensure availability of the medication and to reduce patient waiting time. You should instruct the patient that on his or her return to the office the induction dose will be administered, and that he or she will be monitored in your office. The pharmacist should reiterate this instruction upon filling the prescription. You may wish to limit the prescription to one days' dose, and repeat this method (with or without the coupon) for the first several days of treatment before providing a prescription for several days' supply at one time. Further information regarding this program and a supply of coupons is available by calling our toll-free SUBOXONE Help Line at 1 877 SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com.

Will these coupons and prescriptions be valid at any pharmacy, or will I need to refer patients to a specific store?

The coupons and prescriptions will be valid at any pharmacy. However, prior to prescribing SUBOXONE or SUBUTEX, if you do not maintain a supply of tablets for induction dosing in your office, it is essential that you establish a relationship with one or more specific pharmacies in your area who will be in a position to provide your patients with initial doses as well as instructions for returning to your office for induction and the follow-up prescription. (Such a relationship is also recommended if you intend to maintain initial dosing supplies in your office.) Generally, a pharmacy near your office is recommended for patient convenience. If possible, it is advisable to identify a

pharmacy that will deliver initial doses to your office, so that patients do not have to leave and return for induction dosing. Alternatively, it is recommended that you avail yourself of any call-in or fax-in prescription services provided, to reduce patient waiting time. If you do not currently have a commercial or professional relationship with a pharmacy in your area, we will be pleased to assist in facilitating the establishment of such an arrangement, and to help identify pharmacies with delivery service. Please call our toll-free SUBOXONE Help Line at 1 877 SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com.

Are there special confidentiality issues I should consider?

Remember that you may be communicating with the pharmacist to verify prescriptions for a particular patient. As you may know, there are special federal regulations concerning the confidentiality of substance abuse treatment, records (42 CFR Part 2) and the privacy of health records (HIPAA). To ensure that you will be able to communicate with the pharmacist to confirm the validity of a SUBOXONE or SUBUTEX prescription, it is recommended that you have the patient sign a release of information at the time of the office visit. A sample consent form with all the elements required under 42CFR Part 2 is included with this booklet as an attachment. It is particularly important to obtain the patient's consent if you elect to phone or FAX in prescriptions, as this constitutes disclosure of the patient's treatment. When the prescription is directly transmitted by the physician, there are also prohibitions on the further redisclosure of patient identifying information by the pharmacist. 42CFR Part 2 does not apply when it is the patient who delivers the presciption to the pharmacist, without direct communication from the physician to the pharmacist.

To learn more about these regulations, visit the SAMHSA website www.hipaa.samhsa.gov, or call 1-866-BUP-CSAT

I'm familiar with general principles of addiction treatment, but this is my first experience with office-based prescription of this type of medication. What precautions should I take in my practice to prevent diversion and abuse?

You should consider the following suggestions:

- Initiate treatment with supervised administration, progressing to unsupervised administration as your patient's clinical stability permits.

- Limit the use of Subutex to supervised use, wherever possible. Recall that the Suboxone product contains naloxone, which Subutex does not. The naloxone in Suboxone is likely to precipitate withdrawal symptoms when injected by individuals dependent on heroin, morphine, or other full opiate agonists. Therefore, it is expected that Suboxone will be less attractive to "street addicts" and less likely to be diverted. Therefore, it is strongly recommended that Suboxone be used whenever unsupervised administration is planned.

- As your patients progress, and you consider prescribing Suboxone for take-home use; when determining the size of the prescription you write, you should consider your patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.

- Have plans in place to deal with patient requests for replacement of prescriptions or supplies of medication that are described as lost or stolen.

- Keep tight control of your prescription pads. Never leave them in the examination room, even inside a desk drawer. Never sign an incomplete prescription blank.

- Write all numbers (quantity and strength) in both numbers and letters – like you write your checks.

- Establish a relationship with the pharmacies you expect to be filling your prescriptions for SUBOXONE or SUBUTEX and discuss potential diversion problems and controls with them.

- Request photo (or other) I.D. and Social Security number and maintain copies in patient's record.

- If you suspect an attempt to divert prescription medications, call your local police department.

Where can I get more information on treating patients with Subutex and Suboxone?

- Refer to the physician package insert for prescribing information. Additional recommendations may be found in treatment guidelines available for free from the Center for Substance Abuse Treatment at the Substance Abuse and Mental Health Services Administration. To obtain a copy please call our toll-free SUBOXONE Help Line at 1 877 SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com. Additional information is also available on the CSAT web site at www.dpt.samhsa.gov

- Refer to the package insert for full information on the adverse events seen during the clinical trials using buprenorphine for opiate addiction treatment. Note the important precautions and warnings to share with patients, such as the risk of fatal respiratory depression when buprenorphine is combined with other depressants. Also note other important safety issues such as the fact that buprenorphine should be administered with caution in the elderly or debilitated patient, and those with severe impairment of hepatic, pulmonary or renal function; and that buprenorphine may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during drug induction and dose adjustment

- General information on the treatment of addiction is available through;

The American Academy of Addiction Psychiatry
7301 Mission Road, Suite 252
Prairie Village, KS 66208
Telephone: (913) 262-6161
E-mail: info@aaap.org
Web site: www.aaap.org

The American Society of Addiction Medicine
4601 North Park Ave. Arcade Suite 101
Chevy Chase, MD 20815
Telephone (301) 656-3920
E-mail: email@asam.org
Web site http://asam.org

Substance Abuse and Mental Health
Services Administration
Office of Pharmacologic and Alternative Therapies
CSAT, Rockwall II Building, Suite 740
5600 Fishers Lane
Rockville, MD 20857
Web site: www.dpt.samhsa.gov

Notification of Intent to Use Schedule III, IV, or V Opioid Drugs for the Maintenance and Detoxification Treatment of Opiate Addiction under 21 USC § 823(g)(2)	Form Approved: 0930- 0234 Expiration Date: 10/31/2002 See OMB Statement on Reverse DATE OF SUBMISSION

Note: Notification is required by Sec. 303(g)(2), Controlled Substances Act (21 USC § 823(g)(2)). See instructions on reverse.

1a. **NAME OF PRACTITIONER**

b. State Medical License Number **c. DEA Registration Number**

2. ADDRESS OF PRIMARY LOCATION (*Include Zip Code*)	**3. TELEPHONE NUMBER** (*Include Area Code*) **4. FAX NUMBER** (*Include Area Code*) **5. EMAIL ADDRESS** (*optional*)
6. NAME AND ADDRESS OF GROUP PRACTICE **7. GROUP PRACTICE EMPLOYER IDENTIFICATION NUMBER**	**8. PURPOSE OF NOTIFICATION** (Check all that apply) New Immediate

9. GROUP PRACTITIONERS

NAME _____ **DEA Registration Number**

NAME _____ **DEA Registration Number**

(Include additional pages as necessary to identify each group practice member.)

10. CERTIFICATION OF USE OF NARCOTIC DRUGS UNDER THIS NOTIFICATION

I certify that I will only use schedule III, IV, or V drugs or combinations of drugs that have been approved by the FDA for use in maintenance or detoxification treatment and that have not been the subject of an adverse determination.

11. CERTIFICATION OF QUALIFYING CRITERIA *(Check each appropriate source and provide documentation.)* **I certify that I meet at least one of the following criteria and am therefore a qualifying physician (check and provide documentation for all that apply):**

Subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties
Addiction certification from the American Society of Addiction Medicine
Subspecialty board certification in addiction medicine from the American Osteopathic Association
Completion of not less than eight hours of training for the treatment and management of opiate-dependent patients provided by the following organization(s): Date and location of training
American Society of Addiction Medicine
American Academy of Addiction Psychiatry
American Medical Association
American Osteopathic Association
American Psychiatric Association
Other (specify, include date and location)
Participation as an investigator in one or more clinical trials leading to the approval of a schedule III, IV, or V narcotic drug for maintenance or detoxification treatment
State medical licensing board-approved experience or training in the treatment and management of opiate-dependent patients.
OTHER *(Specify)*

12. CERTIFICATION OF CAPACITY

I certify that I have the capacity to refer patients for appropriate counseling and other appropriate ancillary services.

13. CERTIFICATION OF MAXIMUM PATIENT LOAD

I certify that I or my group practice will not exceed 30 patients for maintenance or detoxification treatment at one time. SMA-167

14. CONSENT TO RELEASE IDENTIFYING INFORMATION TO SAMHSA TREATMENT FACILITY LOCATOR

I consent to the release of my name, address, and phone number to the SAMHSA Treatment Facility Locator.

I do not consent to the release of my name, address, and phone number to the SAMHSA Treatment Facility Locator.

15. I certify that the information presented above is true and correct to the best of my knowledge. I certify that I will notify SAMHSA at the address below if any of the information contained on this form changes. Note: Any false, fictitious, or fraudulent statements or information presented above or misrepresentations relative thereto may violate Federal laws and could subject you to prosecution, and/or monetary penalties, and or denial, revocation or suspension of DEA registration (See 18 U.S.C.§1001; 31 U.S.C.§§3801-3812; 21 U.S.C.§824.)

Signature **Date**

Please send the completed form to:
Substance Abuse and Mental Health Services Administration
Office of Pharmacologic and Alternative Therapies
Attention: Opioid Treatment Waiver Program
CSAT, Rockwall II Building, Suite 740
5600 Fishers Lane
Rockville, MD 20857
Fax 301-443-3994
Phone 301-443-7745

This form is intended to facilitate the implementation of the provisions of 21 USC § 823 (g)(2). The Secretary of DHHS will use the information provided to determine whether practitioners meet the qualifications for waivers from the separate registration requirements under the Controlled Substances Act (21 USC § 823 (g)(1)). The Drug Enforcement Administration will assign an identification number to qualifying practitioners and the number will be included in the practitioner's registration under 21 USC § 823 (f).

This form may be completed and submitted electronically (including facsimile) to facilitate processing.

1. The practitioner must identify the DEA registration number issued under 21 USC§ 823(f) to prescribe substances controlled in Schedules III, IV, or V.	**2. The address should be the primary address listed in the practitioner's registration under § 823(f). Only one address should be specified. If the narcotic drugs or combinations to be used under this notification are to be dispensed by the practitioner then the address must reflect the site where the medication will be dispensed.**

6. Group practice is defined under section 1877(h)(4) of the Social Security Act. **14. The SAMHSA Treatment Facility Locator is freely accessible on the World Wide Web (http://findtreatment.samhsa.gov) and is widely used by the members of the treatment seeking public and referring professionals. It lists more than 11,000 facilities that offer specialized drug and alcohol abuse treatment programs and provides links to many other sources of information on substance abuse. The information on physicians will be retrieved by a geographical search of a separate category within the locator. No disclosures to the SAMHSA Treatment Facility Locator will be made in the absence of express consent.**	**8. Purpose of notification:** **New - an initial notification for a waiver submitted for the purpose of obtaining an identification number from DEA for inclusion in the registration under 21 U.S.C. §823(f).** **Immediate - a notification submitted for the purpose of notifying the Secretary and the Attorney General of the intent to immediately facilitate the treatment of an individual (one) patient.** **Note: It is permissible to submit a new and immediate notification simultaneously.**

PRIVACY ACT INFORMATION

Authority: Section 303 of the Controlled Substances Act of 1970 (21 U.S.C §823(g)(2)).
Purpose: To obtain information required to determine whether a practitioner meets the requirements of 21 U.S.C §823(g)(2).
Routine Uses: Disclosures of information from this system are made to the following categories of users for the purposes stated:
A. Medical specialty societies to verify practitioner qualifications.
B. Other federal law enforcement and regulatory agencies for law enforcement and regulatory purposes.
C. State and local law enforcement and regulatory agencies for law enforcement and regulatory purposes.
D. Persons registered under the Controlled Substance Act (PL 91-513) for the purpose of verifying the registration of customers and practitioners.

Effect: This form was created to facilitate the submission and review of waivers under 21 U.S.C. §823(g)(2). This does not preclude other forms of notification.

Paperwork Reduction Act Statement

Public reporting burden for completing this form is estimated to average 5 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the completed form. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this project is 0930-0234).

SMA-167

Attachment to Physician's Brochure:

SAMPLE 42 CFR Part 2.31 Consent Form

1. I (name of patient) _____{time}
Authorize:
2. Dr._____
3. To disclose: (kind and amount of information to be disclosed)

Any information needed to confirm the validity of my prescription and for submission for payment for the prescription.

_____
4. To: (name or title of the person or organization to which disclosure is to be made)
The dispensing pharmacy to whom I present my prescription or to whom my prescription is called/sent/faxed, as well as to third party payors.

5. For (purpose of the disclosure)
Assuring the pharmacy of the validity of the prescription, so it can be legally dispensed, and for payment purposes.

6. Date (on which this consent is signed)_____
7. Signature of patient _____
8. Signature of parent or guardian (where required)

9. Signature of person authorized to sign in lieu of the patient (where required)

10. This consent is subject to revocation at any time except to the extent that the program which is to make the disclosure has already taken action in reliance on it. If not previously revoked, this consent will terminate upon: (specific date, event, or condition)

Termination of treatment

(c) Expired, deficient, or false consent. A disclosure may not be made on the basis of a consent which: (1) Has expired; (2) On its face substantially fails to conform to any of the requirements set forth in paragraph (a) of this section; (3) Is known to have been revoked; or (4) Is known, or through a reasonable effort could be known, by the person holding the records to be materially false. (Approved by the Office of Management and Budget under control number 0930-0099)

Notice to accompany disclosure:

Each disclosure made with the patient's written consent must be accompanied by the following written statement: This information has been disclosed to you from records protected by Federal confidentiality rules (42 CFR part 2). The Federal rules prohibit you from making any further disclosure of this information unless further disclosure is expressly permitted by the written consent of the person to whom it pertains or as otherwise permitted by 42 CFR part 2. A general authorization for the release of medical or other information is NOT sufficient for this purpose.

Patient Information Leaflet

PATIENT INFORMATION

SUBOXONE® (sub-OX-own)
(buprenorphine HCl/naloxone HCl dihydrate, sublingual tablet) (C*)

SUBUTEX® (SUB-u-tex)
(buprenorphine HCl, sublingual tablet) (C*)

Read this information carefully before you take SUBOXONE or SUBUTEX and each time you get more SUBOXONE or SUBUTEX. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. Only you and your doctor can decide if SUBOXONE or SUBUTEX is right for you. Share the important information in this leaflet with members of your household.

What is the most important information I should know about SUBOXONE and SUBUTEX?

- **SUBOXONE and SUBUTEX can cause death from overdose,** especially if you inject them with tranquilizers. Use SUBOXONE or SUBUTEX exactly the way your doctor tells you to with medicines used to treat depression or anxiety.
- **Use SUBOXONE and SUBUTEX only for the condition for which it was prescribed**.
- **SUBOXONE and SUBUTEX can cause** drug dependence. This means that you can get withdrawal symptoms if you stop using the medicine too quickly. SUBOXONE and SUBUTEX are not for occasional ("as needed") use.
- **Prevent theft and misuse.** SUBOXONE and SUBUTEX contain a narcotic painkiller that can be a target for people who abuse prescription medicines or street drugs. Therefore, keep your tablets in a safe place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is against the law.

- **In an emergency**, have family members tell emergency room staff that you are dependent on opioids (narcotic painkillers) and are being treated with SUBOXONE or SUBUTEX.

What are SUBOXONE and SUBUTEX?

SUBOXONE and SUBUTEX are prescription medicines used to treat adults addicted to opioid (narcotic painkillers) medicines and drugs, such as morphine and heroin. SUBOXONE and SUBUTEX take the place of these medicines and drugs and may help you stop using and abusing them. SUBOXONE and SUBUTEX are part of a complete addiction treatment program that also includes counseling or behavioral therapy.
SUBOXONE and SUBUTEX have not been studied in children.

SUBOXONE is a tablet that contains 2 medicines.

1. The first medicine is called buprenorphine (BYOO-pruh-NOR-feen). It is like painkiller medicines such as morphine, street drugs like heroin, and addiction treatment medicines like methadone. Buprenorphine may give you less of a "high" than these other prescription medicines and street drugs. Withdrawal or stopping buprenorphine may be easier than stopping other prescription medicines and street drugs.
2. SUBOXONE also contains naloxone (nal-OX-own). When naloxone is injected, it blocks the effects of medicines and drugs like methadone, heroin, and morphine. Naloxone is added to SUBOXONE to stop people from injecting ("shooting-up") SUBOXONE tablets. When you use SUBOXONE under your tongue (sublingually), as prescribed, the naloxone in SUBOXONE should not stop the medicine's effects. However, if you inject SUBOXONE, the naloxone can give you bad withdrawal symptoms.

SUBUTEX is a tablet and it contains only the medicine buprenorphine (see "What is SUBOXONE?" for a description of buprenorphine). SUBUTEX is different from SUBOXONE because it does not contain naloxone. It is usually used under a doctor's direct supervision.

Who Should Not Take SUBOXONE or SUBUTEX?

Do not take SUBOXONE or SUBUTEX if

- your doctor did not prescribe SUBUTEX or SUBOXONE for you.
- you are allergic to buprenorphine, or any of the inactive ingredients in the medicines. See the end of this leaflet for a complete list of ingredients.

Do not take SUBOXONE if

- you are allergic to naloxone or buprenorphine.

Your doctor should know about all your medical conditions before deciding if SUBOXONE or SUBUTEX is right for you or what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury or brain problem
- liver or kidney problems
- gallbladder problems
- adrenal gland problems, such as Addison's disease
- low thyroid (hypothyroidism)
- enlarged prostate gland (men)
- problems urinating
- a curve in your spine that affects your breathing
- severe mental problems or hallucinations (seeing or hearing things that are not really there)
- alcoholism

If any of these conditions apply to you, make sure you tell your doctor about them before taking SUBOXONE or SUBUTEX.

Tell your doctor:

- **if you are pregnant or plan to become pregnant**. SUBOXONE **or** SUBUTEX may not be right for you. It is not known whether SUBOXONE or SUBUTEX could harm your baby.
- **if you are breast feeding**. SUBOXONE **or** SUBUTEX will pass through your milk and may harm your baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious side effects when taken with SUBOXONE or SUBUTEX. Sometimes, the doses of certain medicines and SUBOXONE or SUBUTEX need to be reduced if used together.

Do not take any other medicine, herbal, or over-the-counter medicine while using SUBOXONE or SUBUTEX unless your doctor has told you it is okay.

How should I take SUBOXONE or SUBUTEX?

- **Follow your doctor's directions exactly**. Your doctor may change your dose after seeing how the medicine affects you. Do not change your dose unless your doctor

tells you to change it. Do not take SUBOXONE or SUBUTEX more often than prescribed.

- **Put the tablets under your tongue and let them melt**. This will take 2 to 10 minutes. Do not chew or swallow the tablets. The medicine will not work this way and you may get withdrawal symptoms.

- **If your doctor tells you to take more than 1 tablet**, you will be told to:
  - take all tablets at the same time together under your tongue, or take 2 tablets, put them under your tongue. After they melt, put the next tablet or tablets under your tongue right away
  - hold the tablets under your tongue until they melt completely. The medicine will not work if swallowed and you may get withdrawal symptoms.
  - Do not change the way you are told to take your medicine or you may get too little or too much medicine.

- **Do not inject ("shoot-up") SUBOXONE or SUBUTEX.** Shooting-up is dangerous and you may get bad withdrawal symptoms.

- **SUBOXONE and SUBUTEX can cause** withdrawal symptoms if you take them too soon after using drugs like heroin, morphine, or methadone.

- **If you miss a dose** of SUBOXONE or SUBUTEX, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.

- **Before stopping** SUBOXONE or SUBUTEX, ask your doctor how to stop to avoid withdrawal symptoms.

- **If you take too much** SUBOXONE or SUBUTEX or **overdose**, call your local emergency number or poison control center right away.

After you stop taking SUBOXONE or SUBUTEX, flush the unused tablets down the toilet.

What Should I Avoid While Taking SUBOXONE or SUBUTEX?

- **Do not drive, operate heavy machinery, or perform any other dangerous activities** until you know if this medicine affects how alert you are.

- **Do not drink alcohol or take tranquilizers or sedatives** (medicines that help you sleep) while using SUBOXONE or SUBUTEX. **You can die when you use these products** with SUBOXONE or SUBUTEX.
- **Do not take other medicines without talking to your doctor.** Other medicines include prescription and non-prescription medicines, vitamins, and herbal supplements. Be especially careful about medicines that may make you sleepy.

What are the Possible Side Effects of SUBOXONE and SUBUTEX?

Call your doctor or get medical help right away if

- You feel faint, dizzy, confused, or have any other unusual symptoms.
- Your breathing gets much slower than is normal for you.

These can be signs of an overdose or serious problem.

SUBOXONE and SUBUTEX may cause liver problems. Call your doctor right away if:

- Your skin or the white part of your eyes turns yellow (jaundice).
- Your urine turns dark.
- Your bowel movements (stools) turn light in color.
- You don't feel like eating much food for several days or longer.
- You feel sick to your stomach (nausea).
- You have lower stomach pain.

Your doctor will do blood tests while you are taking SUBOXONE or SUBUTEX to make sure your liver is okay.

- **SUBOXONE and SUBUTEX can cause your blood pressure to drop**. This can make you feel dizzy if you get up too fast from sitting or lying down.
- **SUBOXONE and SUBUTEX can cause allergic reactions** that can make it hard for you to breathe. Other symptoms of a bad allergic reaction include hives, swelling of your face, asthma (wheezing) or shock (loss of blood pressure and consciousness). Call a doctor or get emergency help right away if you get any of these symptoms.

You may have withdrawal symptoms when you start treatment with SUBOXONE or SUBUTEX.
You can develop dependence from taking SUBOXONE or SUBUTEX, and so you may get withdrawal symptoms when you stop taking SUBOXONE or SUBUTEX. There is also a chance that you may abuse or get addicted to SUBOXONE or SUBUTEX because SUBOXONE and SUBUTEX are treatments for other drug addictions.

Some of the common side effects of SUBOXONE and SUBUTEX are headache, pain, problems sleeping, nausea, sweating, stomach pain, and constipation.

These are not all the possible side effects of SUBOXONE or SUBUTEX. For a complete list, ask your doctor or pharmacist.

General Information about the safe and effective use of SUBOXONE and SUBUTEX.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use SUBOXONE or SUBUTEX for conditions for which they were not prescribed. Do not give SUBOXONE or SUBUTEX to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems. Keep SUBOXONE and SUBUTEX out of the reach of children. Accidental overdose in children is dangerous and can result in death.

This leaflet summarizes the most important information about SUBOXONE and SUBUTEX. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about SUBOXONE and SUBUTEX that is written for health professionals. For more information call 1-877- SUBOXONE (1-877-782-6966), or visit our Web site, www.suboxone.com.

What are the ingredients of SUBOXONE and SUBUTEX?

SUBOXONE

Active Ingredients: buprenorphine hydrochloride and naloxone hydrochloride dihydrate

Inactive Ingredients: lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate, FD&C Yellow No.6 color, magnesium stearate, and for flavoring, Acesulfame K sweetener and a lemon-lime flavor

SUBUTEX

Active Ingredients: buprenorphine hydrochloride

Inactive Ingredients: lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate and magnesium stearate

RX ONLY

Information for Pharmacists

SUBOXONE® (buprenorphine HCl/naloxone HCl dihydrate, sublingual tablet)

and SUBUTEX® (buprenorphine HCl, sublingual tablet)

What are SUBOXONE and SUBUTEX?

SUBOXONE and SUBUTEX are sublingual tablets indicated for the treatment of opioid dependence. SUBOXONE contains buprenorphine (a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor) and naloxone (an antagonist at the mu-opioid receptor). SUBUTEX contains buprenorphine only.

Why is it important for all pharmacists to learn about SUBOXONE and SUBUTEX?

For the first time, pharmacists will play a role in the delivery of opiate addiction treatment. SUBOXONE and SUBUTEX are the first medications approved for office-based treatment of opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA). Prior to the passage of this law, it was illegal for a doctor to prescribe narcotic drugs for the treatment of narcotic dependence. Opioid dependence treatment of this type could only be provided at specially registered clinics. Under the new law, only opiate addiction treatment drugs under Schedule II are

confined to use in the clinic setting. Less tightly controlled drugs (Schedules III-V) may be *prescribed* for opiate addiction treatment by specially qualified doctors who treat patients in their private offices.

Why are there two formulations?

SUBOXONE is the preferred medication for maintenance treatment due to the presence of naloxone in the formulation, which is intended to deter intravenous abuse by persons dependent on other opiates. SUBUTEX, which does not contain naloxone, may be better tolerated by patients in the first several days of treatment and is generally preferred for induction. "Induction" refers to the initial period of treatment, during which time the patient should receive medication under the doctor's supervision in the office. Patients or their family members may need to come and pick up induction doses each day for the first several days of treatment (or you may be asked to arrange delivery to the doctor's office, if your pharmacy provides this service). Therefore, while you may see prescriptions for small amounts of SUBUTEX presented for induction doses, you should expect the majority of prescriptions to be for SUBOXONE.

SUBOXONE and SUBUTEX are controlled as Schedule III narcotics under the Controlled Substances Act.

How are they supplied?

SUBOXONE is supplied as hexagonal orange tablets in 2 dosage strengths:

2 mg buprenorphine + 0.5 mg naloxone embossed with a sword logo at the midline and N2 on the reverse side

and 8 mg buprenorphine + 2 mg naloxone embossed with a sword logo at the midline and N8 on the reverse side, ,

SUBUTEX is supplied as oval white tablets in in 2 dosage strengths:

2mg buprenorphine embossed with a sword logo at the midline and B2 on the reverse side

and 8mg buprenorphine embossed with a sword logo at the midline and B8 on the reverse side

I've heard that buprenorphine is safer than methadone. Can these drugs be dangerous?

Significant respiratory depression has been associated with buprenorphine, particularly when administered intravenously. A number of deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines concomitantly. Deaths have also been reported in association with concomitant administration of buprenorphine and other depressants such as alcohol or other opioids

Do SUBOXONE and SUBUTEX cause dependence?

Chronic administration of SUBOXONE or SUBUTEX produces dependence of the opiate type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset. Because it contains naloxone, SUBOXONE is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opioid agonists such as

heroin, morphine, or methadone. Sublingually, SUBOXONE may cause opioid withdrawal symptoms in such persons if administered before the agonist effects of the opioid have subsided.

Be sure to read the full Prescribing Information for complete Warnings & Precautions.

What other information should I relay to patients?

It's important that you make sure patients understand their physicians' instructions, and that you answer any questions they may have.

When counseling patients, be sure to discuss any relevant precautions as listed in the Prescribing Information, including but not limited to the following:

- Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on opioids and that the patient is being treated with SUBOXONE or SUBUTEX

- Patients should be cautioned that a serious overdose may occur if benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol are taken at the same time as SUBOXONE or SUBUTEX

- Patients should be cautioned that SUBOXONE or SUBUTEX may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients should be cautioned not to

drive or operate complex machinery until they know how SUBOXONE or SUBUTEX affects their ability to function in these circumstances, such as driving a car.

- Patients should consult their physician if other prescription medications are currently being used or are prescribed for future use

What are the possible side effects of SUBOXONE and SUBUTEX?

The most common adverse events reported in clinical trials with SUBOXONE and SUBUTEX were headache, withdrawal syndrome, pain, nausea, insomnia, sweating, abdominal pain, back pain, constipation, infection, asthenia, rhinitis, anxiety, and depression.

What is the role of the pharmacist in ensuring safe use of SUBOXONE and SUBUTEX?

As a pharmacist, you will play an important role in ensuring that SUBOXONE and SUBUTEX are used safely and appropriately. Each time you fill a prescription for SUBOXONE or SUBUTEX, make sure to:

- Verify that the prescriptions you receive are from physicians who are in compliance with the provisions of the DATA (see below).

- Remind patients who are picking up induction doses to return as directed to the doctor's office so that they can be supervised while taking the medication.

- Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple suppliers.

Who is qualified to prescribe SUBOXONE and SUBUTEX?

The DATA limits office-based use of SUBOXONE and SUBUTEX to physicians who meet special training criteria and can provide appropriate services. To be qualified, physicians must:

- Meet one or more of the following training requirements
  - Hold a subspecialty board certification in addiction psychiatry from the American Board of medical Specialties

  - Hold a subspecialty board certification in Addiction Medicine from the American Osteopathic Association

  - Hold an addiction certification from the American Society of Addiction Medicine

  - Have completed not less than 8 hours of authorized training on the treatment or management of opioid-dependent patients. This training may include classroom situations, seminars at professional society meetings, electronic communications, or other media. The American Society of Addiction Medicine,-The American Academy of Addiction Psychiatry, the American Medical Association, the

American Osteopathic Association, and the American Psychiatric Association are all authorized to provide this training.

- AND meet both of the following criteria:
  - Have the capacity to provide or to refer patients for necessary ancillary services, such as psychosocial therapy.

  - Agree to treat no more than 30 patients at any one time in their individual or group practice

How can I be sure a physician is qualified to prescribe SUBOXONE and SUBUTEX?

Physicians who meet the qualification criteria listed in the previous section must also notify the Secretary of Health & Human Services of their intent to prescribe SUBOXONE and SUBUTEX before doing so. Once all relevant criteria are verified, DEA will issue the physician a unique identification number indicating that he or she is a qualifying physician under the DATA. The Center for Substance Abuse Treatment (CSAT, a component of the Substance Abuse and Mental Health Services Administration) will send a letter informing the physician of the new DEA identification number. The physicians will subsequently receive a revised DEA registration certificate (showing both numbers).

Pharmacists who seek information to verify whether or not physicians have valid waivers may contact 1-866-BUP-CSAT, or by email at info@buprenorphine.samhsa.gov

What if I get a prescription from a doctor who does not have a special DEA identification number?

Call that physician for clarification that the physician has made the appropriate notification to DHHS. DEA is developing regulations that will require this number along with the physician's existing DEA registration number to be included on all prescriptions issued

for the treatment of opioid dependence; therefore physicians are being strongly urged to include this number on prescriptions.

Most physicians will make arrangements to obtain the identification number before prescribing SUBOXONE or SUBUTEX, but in rare cases a physician may need to write a prescription before the number has been issued. This is allowed under the DATA provided the physician has notified the Department of Health and Human Services of his/her intention to begin treating a patient right away; the notification form includes a check box for this situation.

Are there confidentiality issues I should be aware of related to substance abuse treatment?

There are special federal regulations concerning the confidentiality of substance abuse treatment records (42 CFR Part 2) and the privacy of health records(HIPAA)which may come into play in your interactions with physicians to verify prescriptions for SUBOXONE and SUBUTEX. To ensure that physicians will be able to communicate with you to confirm the validity of a SUBOXONE or SUBUTEX prescription, it is recommended that the physician have the patient sign a release of information at the time of the office visit. A sample consent form with all the elements required under 42 CFR Part 2 is included with this booklet as an attachment. It is particularly important to obtain the patient's consent if the physician elects to phone or FAX in prescriptions, as this constitutes disclosure of the patient's treatment. When the prescription is directly transmitted by the physician, there are also prohibitions on the further redisclosure of patient identifying information by the pharmacist. 42CFR Part 2 does not apply when it is the patient who delivers the presciption to

the pharmacist, without direct communication from the physician to the pharmacist.

To learn more about these regulations, visit the SAMHSA website www.hipaa.samhsa.gov, or call 1-866-BUP-CSAT for information.

Again, Pharmacists who seek information to verify whether or not physicians have valid waivers may contact 1-866-BUP-CSAT, or by email at info@buprenorphine.samhsa.gov

How will physicians obtain supplies of medication for induction?

Because induction doses of SUBOXONE and SUBUTEX should be given in the physician's office, many physicians will maintain a supply of each medication in their office. Most physicians will get this supply through their normal supplier or the manufacturer. Some physicians, however, will write prescriptions for individual patients' induction doses at the time of the patient appointment. The prescribing physician may call or fax ahead to your pharmacy to request delivery (if you provide this service), or to ensure the medication will be ready in advance of the patient's arrival. (Recall that the patient is likely to be in mild withdrawal while awaiting the prescription.) Some physicians may send a patient's family member to the pharmacy to pick up the induction dose.

What should I do when a patient presents a prescription for an induction dose?

Physicians who choose not to maintain supplies of SUBOXONE or SUBUTEX in their offices may give their patients a prescription for their induction doses with instructions to return to the office for supervision while the dose is administered. Fill the prescription as

you normally would, then make sure the patient understands that he or she must return to the doctor's office to take the medication. It may take several days of supervised administration to complete the induction process, therefore, some patients may be visiting your pharmacy repeatedly at the beginning of treatment.

Where state laws allow, patients may be provided with a coupon that covers the cost of the first day's dose. The coupon presented to you by the patient can be submitted to reimburse the cost of the medication.

Are there any special storage, record-keeping, or other requirements associated with SUBOXONE and SUBUTEX?

As Schedule III controlled substances, SUBOXONE and SUBUTEX are subject to certain federal regulations covering areas such as record-keeping, inventory, proper dispensing and disposal. These are explained in the Drug Enforcement Administration's Pharmacist's Manual, which can be found at **www.deadiversion.usdoj.gov/pubs/manuals/pharm2/index.htm.**

Many states have their own, additional requirements for pharmacists dispensing controlled substances. Be sure to check with the appropriate authority in your state. For more information, visit the website of the National Association of Boards of Pharmacy at www.nabp.org for links to individual state boards of pharmacy.

In addition, since drug addiction is a sensitive topic, you should make sure you have access to a private area in which to counsel patients about SUBOXONE and SUBUTEX therapy. When

speaking with these patients, it is important to keep in mind that addicts in withdrawal may be irritable and short on patience.

What else can I do to help safeguard against diversion?

According to federal law, pharmacists and prescribers jointly share legal responsibility for the legitimacy of a prescription. Communication between you and the prescriber is vital to ensure the validity of each prescription you're asked to fill.

However, even if you determine that an individual prescription is legal, you should still be aware of other means by which addicts may attempt to divert their prescriptions. For example, an opioid user may present to 2 or more qualified prescribers, and therefore receive multiple prescriptions for SUBOXONE or SUBUTEX. If a patient brings you more than 1 prescription covering the same therapeutic period, you have a legal duty to recognize that they are probably not for therapeutic use. You should refuse to fill the second prescription, and notify both prescribing physicians.

In addition, you should be aware that the DATA allows each physician to treat no more than 30 patients with buprenorphine at any one time. Obviously, as patients enter and leave treatment, more than 30 patients will be cared for by a particular physician over the course of time. However, if you notice an extraordinary number of new prescriptions from a single physician, you may wish to check with the prescriber to determine whether the prescriptions might be fraudulent.

Where can I get more information on treating opioid addiction with SUBOXONE and SUBUTEX?

- Refer to the package insert for full information on the adverse events seen during the clinical trials using buprenorphine for opiate addiction treatment.

- Clinical guidelines for buprenorphine treatment and general information on the treatment of addiction is available through numerous sources such as the following: Substance Abuse and Mental Health Services (SAMHSA) Center for Substance Abuse Treatment (CSAT) Web site at www.dpt.samhsa.gov American Society of Addiction Medicine Web site at **www.asam.org/** and the American Academy of Addiction Psychiatry website at **www.aaap.org/**

For more information, call our toll-free help line at 1-877-SUBOXONE (1-877-782-6966) or visit our Web site at www.suboxone.com.

Please see enclosed full Prescribing Information

Attachment to Pharmacist Brochure:

SAMPLE 42 CFR Part 2.31 Consent Form

2. I (name of patient) _____{time}
Authorize:
2. Dr._____
3. To disclose: (kind and amount of information to be disclosed)

Any information needed to confirm the validity of my prescription and for submission for payment for the prescription.

4. To: (name or title of the person or organization to which disclosure is to be made)
The dispensing pharmacy to whom I present my prescription or to whom my prescription is called/sent/faxed, as well as to third party payors.

5. For (purpose of the disclosure)
Assuring the pharmacy of the validity of the prescription, so it can be legally dispensed, and for payment purposes.

6. Date (on which this consent is signed)_____
7. Signature of patient _____
8. Signature of parent or guardian (where required)

9. Signature of person authorized to sign in lieu of the patient (where required)

10. This consent is subject to revocation at any time except to the extent that the program which is to make the disclosure has already taken action in reliance on it. If not previously revoked, this consent will terminate upon: (specific date, event, or condition)

Termination of treatment

(c) Expired, deficient, or false consent. A disclosure may not be made on the basis of a consent which: (1) Has expired; (2) On its face substantially fails to conform to any of the requirements set forth in paragraph (a) of this section; (3) Is known to have been revoked; or (4) Is known, or through a reasonable effort could be known, by the person holding the records to be materially false. (Approved by the Office of Management and Budget under control number 0930-0099).

Notice to accompany disclosure:

Each disclosure made with the patient's written consent must be accompanied by the following written statement: This information has been disclosed to you from records protected by Federal confidentiality rules (42 CFR part 2). The Federal rules prohibit you from making any further disclosure of this information unless further disclosure is expressly permitted by the written consent of the person to whom it pertains or as otherwise permitted by 42 CFR part 2. A general authorization for the release of medical or other information is NOT sufficient for this purpose.